

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 10:12:14 ON 05 OCT 2004
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FILE COVERS 1907 - 5 Oct 2004 VOL 141 ISS 15
FILE LAST UPDATED: 4 Oct 2004 (20041004/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil medline

FILE 'MEDLINE' ENTERED AT 10:12:18 ON 05 OCT 2004

FILE LAST UPDATED: 2 OCT 2004 (20041002/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLD MEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil embase

FILE 'EMBASE' ENTERED AT 10:12:20 ON 05 OCT 2004
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FILE COVERS 1974 TO 30 Sep 2004 (20040930/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil biosis

FILE 'BIOSIS' ENTERED AT 10:12:23 ON 05 OCT 2004
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FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNS) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 29 September 2004 (20040929/ED)

FILE RELOADED: 19 October 2003.

=> fil caba

FILE 'CABA' ENTERED AT 10:12:29 ON 05 OCT 2004
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FILE COVERS 1973 TO 3 Sep 2004 (20040903/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

=> fil confsci

FILE 'CONFSCI' ENTERED AT 10:12:33 ON 05 OCT 2004
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FILE COVERS 1973 TO 23 Sep 2004 (20040923/ED)

=> fil pascal

FILE 'PASCAL' ENTERED AT 10:12:37 ON 05 OCT 2004
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FILE LAST UPDATED: 4 OCT 2004 <20041004/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE
IN THE BASIC INDEX (/BI) FIELD <<<

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 10:12:42 ON 05 OCT 2004
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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 1, 2004 (20041001/UP).

=>

FILE 'MEDLINE, BIOSIS, PASCAL, CABA, CONFSCI, EMBASE, HCAPLUS' ENTERED AT
10:03:22 ON 05 OCT 2004
L37 13867 SEA ABB=ON PLU=ON ANDERSON, C?/AU

=>

=> d his 137-146

(FILE 'MEDLINE, BIOSIS, PASCAL, CABA, CONFSCI, EMBASE, HCAPLUS' ENTERED
AT 10:03:22 ON 05 OCT 2004)

L37 13867 S ANDERSON, C?/AU
L38 23965 S DAVIS, R?/AU
L39 144 S CLEVENGER, W?/AU
L40 250 S WILEY, S?/AU
L41 20131 S MILLER, S?/AU
L42 1591 S SZABO, T?/AU
L43 14733 S GHOSH, S?/AU
L44 544 S MOOS, W?/AU
L45 1870 S PEI, Y?/AU
L46 76735 S L37-L45

=> d que 155

L37 13867 SEA ANDERSON, C?/AU
L38 23965 SEA DAVIS, R?/AU
L39 144 SEA CLEVENGER, W?/AU
L40 250 SEA WILEY, S?/AU
L46 76735 SEA (L37 OR L38 OR L39 OR L40 OR L41 OR L42 OR L43 OR L44 OR
L45)
L47 3284 SEA ?ATRACTYLOSID?
L48 10 SEA L46 AND L47
L49 45697 SEA ANT OR ((ATP(1W) ADP) (2A) (?CARR? OR ?TRANSLO?))
L50 68 SEA L46 AND L49
L51 75 SEA L48 OR L50
L52 47 DUP REM L51 (28 DUPLICATES REMOVED)
L55 9 SEA L52 AND L47

=> d 155 ibib abs 1-9

YOU HAVE REQUESTED DATA FROM FILE 'EMBASE, HCAPLUS' - CONTINUE? (Y)/N:y

L55 ANSWER 1 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2003333979 EMBASE

TITLE: Design and combinatorial synthesis of N-acyl iminodiacetic
acids as bongkreikic acid analogues for the inhibition of
adenine nucleotide translocase.

AUTHOR: **Pei Y.**; Carroll A.K.; **Anderson C.M.**;
Moos W.H.; **Ghosh S.S.**

CORPORATE SOURCE: Y. Pei, MitoKor, Inc., 11494 Sorrento Valley Road, San
Diego, CA 92121, United States. peiy@mitokor.com

SOURCE: Synthesis, (2003) -/11 (1717-1721).

Refs: 17

ISSN: 0039-7881 CODEN: SYNTBF

COUNTRY: Germany

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The adenine nucleotide translocase (**ANT**) mediates ADP/ATP
exchange in mitochondria and is also a critical component of the
mitochondrial permeability transition (MPT) pore. Opening of this

physiological pore has been implicated as a key step in initiating cell death, hence agents that prevent MPT pore opening may be of potential therapeutic value. The natural product bongkrekic acid is a potent **ANT** inhibitor that is reported to block MPT opening. We present the design and synthesis of N-acyl iminodiacetic acids as novel inhibitors of **ANT**-1, using bongkrekic acid as an initial lead. The identification of potent **ANT**-1 inhibitors from a primary binding assay and the preliminary structure-activity relationship based on these new leads are discussed.

L55 ANSWER 2 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2002161075 EMBASE
TITLE: High-throughput assessment of mitochondrial membrane potential in situ using fluorescence resonance energy transfer.

AUTHOR: Dykens J.A.; Fleck B.; Ghosh S.; Lewis M.;
Velicelebi G.; Ward M.W.

CORPORATE SOURCE: J.A. Dykens, MitoKor, 11494 Sorrento Valley Road, San
Diego, CA 92121, United States. dykensj@mitokor.com

SOURCE: Mitochondrion, (2002) 1/5 (461-473).

Refs: 52

ISSN: 1567-7249

PUBLISHER IDENT.: S 1567-7249(02)00011-9

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

030 Pharmacology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Mitochondrial dysfunction causes dozens of debilitating diseases, and is implicated in the etiology of type 2 diabetes, Parkinson's and Alzheimer's diseases, among others. However, development of mitochondrially targeted therapeutic agents has been impeded by the lack of high-throughput screening techniques that are capable of distinguishing in intact cells the mitochondrial membrane potential ($\Delta\psi(p)$) from the plasma membrane potential, ($\Delta\psi(p)$). We report here a fluorescence resonance energy transfer (FRET) assay that specifically monitors $\Delta\psi(p)$ that is not confounded by background signal arising from potentiometric dye responding to $\Delta\psi(p)$. The technique relies on energy transfer between nonyl acridine orange (NAO), which stains diphosphatidyl glycerol (cardiolipin) that is indigenous to the inner mitochondrial membrane, and tetramethylrhodamine methyl ester (TMR), a potentiometric dye that is sequestered by mitochondria as a Nernstian function of $\Delta\psi(m)$ and concentration. FRET occurs only when both dyes co-localize to the mitochondria, and results in quenching of NAO emission by TMR in proportion to $\Delta\psi(m)$. Validation studies using compounds with well-characterized mitochondrial effects, including oligomycin, CCCP(+), bongkrekic acid, cyclosporin A, nigericin, ADP, and ruthenium red, demonstrate that the FRET-based $\Delta\psi(m)$ assay responds in accord with the known pharmacology. Validation studies assessing the suitability of the technique for high-throughput compound screening indicate that the assay provides a sensitive and robust assessment not only of mitochondrial integrity in situ, but also, when used in conjunction with agents such as cyclosporin A, an indicator of permeability transition. .COPYRG. 2002 Elsevier Science B.V. and Mitochondria Research Society. All rights reserved.

L55 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:833514 HCAPLUS
 DOCUMENT NUMBER: 136:1609
 TITLE: Production of adenine nucleotide translocator (**ANT**) with recombinant cells, **ANT** ligands and screening assays therefor
 INVENTOR(S): **Anderson, Christen M.; Davis, Robert E.; Clevenger, William; Wiley, Sandra Eileen; Miller, Scott W.; Szabo, Tomas R.; Ghosh, Soumitra S.; Moos, Walter H.; Pei, Yazhong;**
 Carroll, Amy K.
 PATENT ASSIGNEE(S): Mitokor, USA
 SOURCE: PCT Int. Appl., 147 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001085944	A2	20011115	WO 2001-US15416	20010511
WO 2001085944	A3	20020829		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1283884	A2	20030219	EP 2001-935420	20010511
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2003532420	T2	20031105	JP 2001-582533	20010511
PRIORITY APPLN. INFO.:			US 2000-569327	A 20000511
			WO 2001-US15416	W 20010511

OTHER SOURCE(S): MARPAT 136:1609

AB Compsns. and methods are provided for producing adenine nucleotide translocator (**ANT**) polypeptides and fusion proteins, including the production and use of recombinant expression constructs having a regulated promoter. **ANT** ligands and compsns. and methods for identifying **ANT** ligands, agents that bind **ANT** and agents that interact with **ANT** are also disclosed. Thus, **ANT** cDNAs were expressed in Sf9 and E.coli. Fluorescent and radiolabeled derivs. of **atractyloside** were prepared Binding of these derivs. to **ANT** was examined

L55 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:338715 HCAPLUS
 DOCUMENT NUMBER: 134:349692
 TITLE: Determining interactions of cyclophilin D and the adenine nucleotide translocator to assess mitochondrial permeability and in screening permeability altering substances
 INVENTOR(S): **Murphy, Anne N.; Clevenger, William; Wiley, Sandra E.; Andreyev, Alexander Y.; Frigeri, Luciano G.; Velicelebi, Gonul; Davis, Robert E.**

PATENT ASSIGNEE(S): Mitokor, USA
SOURCE: PCT Int. Appl., 186 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032876	A2	20010510	WO 2000-US30535	20001103
WO 2001032876	A3	20020117		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6562563	B1	20030513	US 1999-434354	19991103
EP 1228206	A2	20020807	EP 2000-975595	20001103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003516128	T2	20030513	JP 2001-535558	20001103
PRIORITY APPLN. INFO.: US 1999-434354 A 19991103				
WO 2000-US30535 W 20001103				
AB A method of measuring transitions in mitochondrial membrane permeability by assessing the interaction of the mitochondrial adenine nucleotide translocator and cyclophilin D is described. The method can be used to screen for permeability altering agents for use, for example, in the treatment of a variety of conditions associated with altered mitochondrial function. Hexahistidine-labeled ANT3 adenine nucleotide translocator manufactured by expression of the cloned gene in Trichoplusia ni cells was immobilized on nickel-containing agarose beads. Cyclophilin D was manufactured as a fusion protein with glutathione-S-transferase. The cyclophilin D fusion product was incubated with the bead immobilized ANT3 and the bound cyclophilin D was determined by immunoassay of the glutathione-S-transferase moiety. The interaction showed the expected properties.				
L55 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN				
ACCESSION NUMBER: 2001:168189 HCAPLUS				
DOCUMENT NUMBER: 134:219377				
TITLE: Methods for assaying mitochondrial intermembrane space protein translocation and drug screening				
INVENTOR(S): Murphy, Anne N.; Wiley, Sandra Eileen; Andreyev, Alexander Y.				
PATENT ASSIGNEE(S): Mitokor, USA				
SOURCE: PCT Int. Appl., 70 pp. CODEN: PIXXD2				
DOCUMENT TYPE: Patent				
LANGUAGE: English				
FAMILY ACC. NUM. COUNT: 1				
PATENT INFORMATION:				

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001016373	A2	20010308	WO 2000-US23638	20000828

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-151231P P 19990827
 US 1999-169508P P 19991207
 US 2000-606370 A 20000628

AB Compns. and methods are provided for identifying agents that alter mitochondrial intermembrane space protein (MISP) translocation. The screening methods generally detect agents that alter the level of detectable extramitochondrial MISP following exposure of a cell to an agent known or suspected to induce mitochondrial intermembrane space protein translocation. Such agents may be used, for example, in the treatment of a variety of conditions associated with altered mitochondrial function. SH-SY5Y neuroblastoma cells were transfected with a recombinant expression construct encoding adenylate kinase-2 fusion protein with hemagglutinin epitope tag. Several stable cell lines were established that overexpress the fusion protein. The cells were treated with various apoptogens, harvested, and analyzed by Western blot for cytochrome c and adenylate kinase release from the mitochondria.

L55 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:911534 HCAPLUS

DOCUMENT NUMBER: 134:66121

TITLE: Compositions and methods for assaying subcellular conditions and processes using energy transfer for drug screening

INVENTOR(S): Dykens, James A.; Velicelebi, Gonul; Ghosh, Soumitra S.

PATENT ASSIGNEE(S): Mitokor, USA

SOURCE: PCT Int. Appl., 189 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000079274	A2	20001228	WO 2000-US17380	20000622
WO 2000079274	A3	20020110		
W:				
AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:				
GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6323039	B1	20011127	US 1999-338122	19990622
US 6280981	B1	20010828	US 2000-514569	20000223
EP 1210596	A2	20020605	EP 2000-943119	20000622
R:				
AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

JP 2003506014 T2 20030218 JP 2001-505191 20000622
 PRIORITY APPLN. INFO.: US 1999-140433P P 19990622
 US 1999-338122 A 19990622
 US 2000-176383P P 20000114
 WO 2000-US17380 W 20000622

AB The invention provides compns. and methods for monitoring subcellular compartments such as organelles by energy transfer techniques that do not require specific intermol. affinity binding events between energy transfer donor and energy transfer acceptor mols. pH. Provided are methods for assaying cellular membrane potential, including mitochondrial membrane potential, by energy transfer methodologies including fluorescence resonance energy transfer (FRET). Diagnostic and drug screening assays are also provided.

L55 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:314834 HCAPLUS

DOCUMENT NUMBER: 132:344104

TITLE: Cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands

INVENTOR(S): Anderson, Christen M.; Davis, Robert E.; Clevenger, William; Wiley, Sandra Eileen; Miller, Scott W.; Szabo, Tomas R.; Ghosh, Soumitra S.

PATENT ASSIGNEE(S): Mitokor, USA

SOURCE: PCT Int. Appl., 175 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000026370	A2	20000511	WO 1999-US25883	19991103
WO 2000026370	A3	20001116		
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1049780	A1	20001108	EP 1999-968032	19991103
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP 2002539761	T2	20021126	JP 2000-579742	19991103
AU 769756	B2	20040205	AU 2000-24729	19991103
US 2001044144	A1	20011122	US 2001-811094	20010314
US 2002012992	A1	20020131	US 2001-810644	20010314
JP 2004154139	A2	20040603	JP 2003-408115	20031205
PRIORITY APPLN. INFO.:			US 1998-185904	A 19981103
			US 1999-393441	A 19990908
			JP 2000-579742	A3 19991103
			WO 1999-US25883	W 19991103

OTHER SOURCE(S): MARPAT 132:344104

AB Compns. and methods are provided for producing adenine nucleotide translocator (ANT) polypeptides and fusion proteins, including

the production and use of recombinant expression constructs having a regulated promoter. Bacterial, insect, yeast (Sf9 cells and Trichoplusia ni cells), and mammalian expression systems are designed for reliable production of recombinant human **ANT** polypeptides in significant quantities, by employing regulated promoters and recombinant **ANT** fusion products with glutathione S-transferase and green fluorescent protein. The synthesis and properties of representative **atractyloside** derivs. as **ANT** ligands are described. **ANT** ligands and compns. and methods for identifying **ANT** ligands, agents that bind **ANT**, and agents that interact with **ANT** are also disclosed.

L55 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:227858 HCAPLUS

DOCUMENT NUMBER: 132:260666

TITLE: Identifying agents that alter mitochondrial permeability transition pores and cell death for diagnostic and therapeutic use

INVENTOR(S): Dykens, James A.; Miller, Scott W.; Ghosh, Soumitra S.; Davis, Robert E.

PATENT ASSIGNEE(S): Mitokor, USA

SOURCE: PCT Int. Appl., 88 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000019200	A1	20000406	WO 1999-US22261	19990924
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2003044776	A1	20030306	US 1998-161172	19980925
CA 2345066	AA	20000406	CA 1999-2345066	19990924
AU 9961628	A1	20000417	AU 1999-61628	19990924
EP 1116027	A1	20010718	EP 1999-948458	19990924
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525630	T2	20020813	JP 2000-572655	19990924
PRIORITY APPLN. INFO.:			US 1998-161172	A 19980925
			WO 1999-US22261	W 19990924

AB Methods are provided for identifying agents that affect mitochondrial functions and cell death. Such agents are useful for treating diseases associated with mitochondrial dysfunction and in methods of identifying a risk or presence of such diseases. In particular, the invention relates to the loss of mitochondrial membrane potential ($\Delta\Psi_m$) during mitochondrial permeability transition (MPT) and further provides a measurable rate loss function, changes in which are useful e.g. for detecting agents that affect one or more mitochondrial functions, for detecting mitochondrial diseases, and for studying mol. components of mitochondria that regulate MPT.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1984:206474 HCAPLUS

DOCUMENT NUMBER: 100:206474

TITLE: Toxic constituents in Mongolian xanthium (Xanthium mongolicum) kernel

AUTHOR(S): Wang, Suxian; Ren, Lijuan; Sun, Zeren; **Pei, Yuehu**; Zhu, Tingru

CORPORATE SOURCE: Shengyang Coll. Pharm., Shanyang, Peop. Rep. China

SOURCE: Zhongcaoyao (1983), 14(12), 529-31

CODEN: CTYAD8; ISSN: 0253-2670

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

GI For diagram(s), see printed CA Issue.

AB A toxic glycoside, **atractyloside** (I), was isolated from a hot water extract of defatted powdered seeds of *X. mongolicum* 1st by successive treatment and precipitation with 50% EtOH, 70% acetone, and 10% Pb acetate, followed by filtration; the filtrate was washed with H₂S to remove Pb and I was crystallized with 70% EtOH. The structure of I was determined by chemical and spectral methods.

=> FIL STNGUIDE

FILE 'STNGUIDE' ENTERED AT 10:16:19 ON 05 OCT 2004

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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Oct 1, 2004 (20041001/UP).

=>

=> fil lreg

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LREGISTRY IS A STATIC LEARNING FILE

=> fil reg

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provided by InfoChem.

STRUCTURE FILE UPDATES: 4 OCT 2004 HIGHEST RN 756793-93-8
DICTIONARY FILE UPDATES: 4 OCT 2004 HIGHEST RN 756793-93-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> fil hcap

FILE 'HCAPLUS' ENTERED AT 09:20:47 ON 05 OCT 2004
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FILE COVERS 1907 - 5 Oct 2004 VOL 141 ISS 15
FILE LAST UPDATED: 4 Oct 2004 (20041004/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> fil uspatfull

FILE 'USPATFULL' ENTERED AT 09:20:53 ON 05 OCT 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 30 Sep 2004 (20040930/PD)
FILE LAST UPDATED: 30 Sep 2004 (20040930/ED)
HIGHEST GRANTED PATENT NUMBER: US6799328
HIGHEST APPLICATION PUBLICATION NUMBER: US2004194186
CA INDEXING IS CURRENT THROUGH 30 Sep 2004 (20040930/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 30 Sep 2004 (20040930/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2004

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>>> USPAT2 is now available. USPATFULL contains full text of the    <<<
>>> original, i.e., the earliest published granted patents or      <<<
>>> applications. USPAT2 contains full text of the latest US       <<<
>>> publications, starting in 2001, for the inventions covered in   <<<
>>> USPATFULL. A USPATFULL record contains not only the original   <<<
>>> published document but also a list of any subsequent           <<<
>>> publications. The publication number, patent kind code, and    <<<
>>> publication date for all the US publications for an invention  <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc.                                                       <<<
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>>> USPATFULL and USPAT2 can be accessed and searched together    <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to       <<<
>>> enter this cluster.                                           <<<
>>>                                                                <<<
>>> Use USPATALL when searching terms such as patent assignees,    <<<
>>> classifications, or claims, that may potentially change from  <<<
>>> the earliest to the latest publication.                       <<<
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This file contains CAS Registry Numbers for easy and accurate
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=> fil medline

FILE 'MEDLINE' ENTERED AT 09:20:59 ON 05 OCT 2004

FILE LAST UPDATED: 2 OCT 2004 (20041002/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
for details. OLD MEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and
http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
description of changes.

This file contains CAS Registry Numbers for easy and accurate
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=> fil biosis

FILE 'BIOSIS' ENTERED AT 09:21:03 ON 05 OCT 2004
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNS) PRESENT

FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 29 September 2004 (20040929/ED)

FILE RELOADED: 19 October 2003.

=> fil embase

FILE 'EMBASE' ENTERED AT 09:21:05 ON 05 OCT 2004
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FILE COVERS 1974 TO 30 Sep 2004 (20040930/ED)

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=> fil wpix

FILE 'WPIX' ENTERED AT 09:21:08 ON 05 OCT 2004
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FILE LAST UPDATED: 1 OCT 2004 <20041001/UP>
MOST RECENT DERWENT UPDATE: 200463 <200463/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

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<http://thomsonderwent.com/coverage/latestupdates/> <<<

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GUIDES, PLEASE VISIT:
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DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
FIRST VIEW - FILE WPIFV.
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HIT STRUCTURES WITHIN THE BIBLIOGRAPHIC DOCUMENT <<<

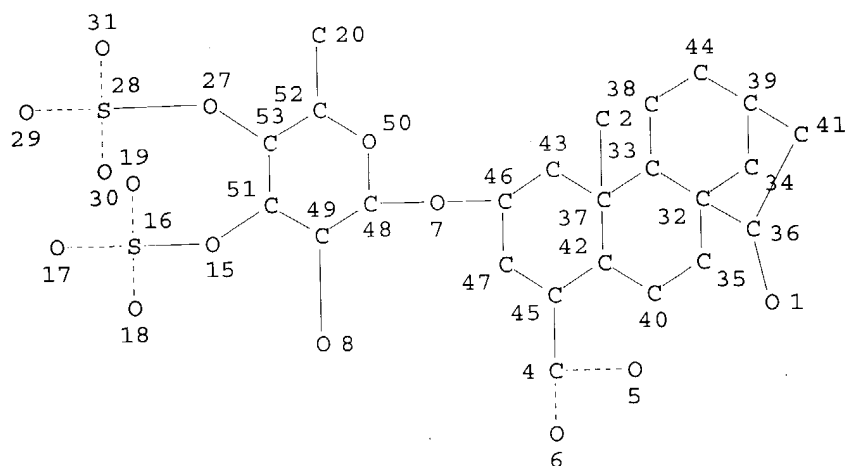
=> file stnguide

FILE 'STNGUIDE' ENTERED AT 09:21:11 ON 05 OCT 2004
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 1, 2004 (20041001/UP).

=> d que 115

L5 STR

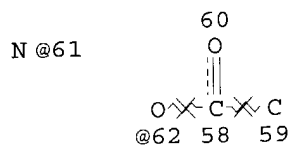
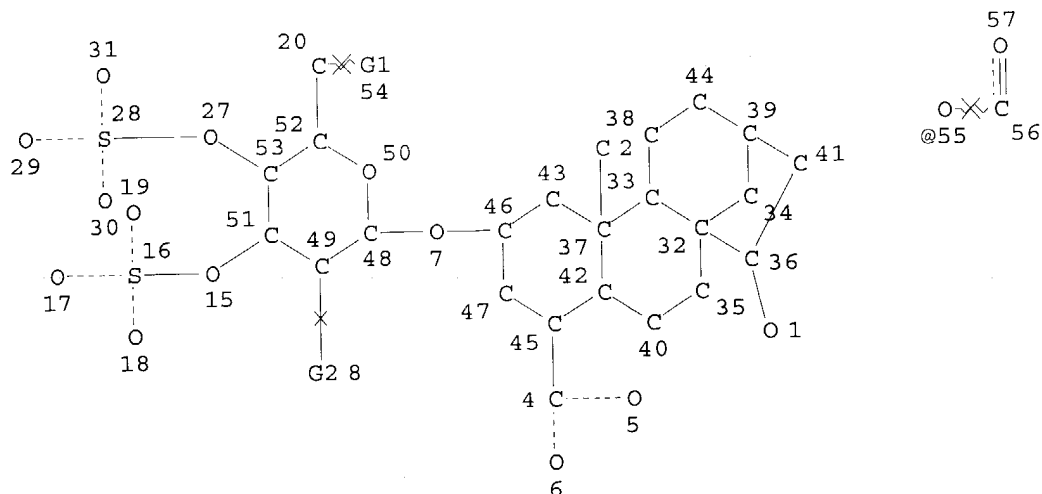


NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 40

STEREO ATTRIBUTES: NONE

L9 100 SEA FILE=REGISTRY SSS FUL L5
 L12 STR



VAR G1=X/55/61
 VAR G2=OH/62
 NODE ATTRIBUTES:

NSPEC IS RC AT 59
NSPEC IS RC AT 61
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 49

STEREO ATTRIBUTES: NONE

L15 65 SEA FILE=REGISTRY SUB=L9 SSS FUL L12

=> d que nos 119

L5 STR
L9 100 SEA FILE=REGISTRY SSS FUL L5
L12 STR
L15 65 SEA FILE=REGISTRY SUB=L9 SSS FUL L12
L19 17 SEA FILE=HCAPLUS ABB=ON PLU=ON L15

=> d que nos 120

L5 STR
L9 100 SEA FILE=REGISTRY SSS FUL L5
L12 STR
L15 65 SEA FILE=REGISTRY SUB=L9 SSS FUL L12
L20 4 SEA FILE=USPATFULL ABB=ON PLU=ON L15

=> d que nos 121

L5 STR
L9 100 SEA FILE=REGISTRY SSS FUL L5
L12 STR
L15 65 SEA FILE=REGISTRY SUB=L9 SSS FUL L12
L21 2 SEA FILE=MEDLINE ABB=ON PLU=ON L15

=>

FILE 'BIOSIS, EMBASE' ENTERED AT 09:06:58 ON 05 OCT 2004

=> d que 132

L22 1349 SEA ?ATRACTYLOSID?
L25 18420 SEA ANT OR ((ATP(1W) ADP) (2A) (?CARR? OR ?TRANSLO?))
L27 100 SEA L22 (L) L25
L29 61 SEA L27 AND (PY<2000 OR MY<2000)
L30 46 SEA L22 (7A) L25
L31 26 SEA L29 AND L30
L32 19 DUP REM L31 (7 DUPLICATES REMOVED)

=> d que 135

L33 13 SEA FILE=WPIX ABB=ON PLU=ON (?ATRACTYLOSID? OR ?ATRACTYLO
SID? OR ?ATRACTYL OSID? OR ?ATRAC TYLOSID?)/BIX
L34 3869 SEA FILE=WPIX ABB=ON PLU=ON (ANT OR ((ATP(1W)ADP) (2A)
(?CARR? OR ?TRANSLO? OR ?TRANS LOC?)))/BIX
L35 7 SEA FILE=WPIX ABB=ON PLU=ON L33 AND L34

=> dup rem 119 120 121 132 135

FILE 'HCAPLUS' ENTERED AT 09:22:31 ON 05 OCT 2004
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PROCESSING COMPLETED FOR L21
PROCESSING COMPLETED FOR L32
PROCESSING COMPLETED FOR L35
L36 46 DUP REM L19 L20 L21 L32 L35 (3 DUPLICATES REMOVED)
ANSWERS '1-17' FROM FILE HCAPLUS
ANSWERS '18-21' FROM FILE USPATFULL
ANSWER '22' FROM FILE MEDLINE
ANSWERS '23-37' FROM FILE BIOSIS
ANSWERS '38-41' FROM FILE EMBASE
ANSWERS '42-46' FROM FILE WPIX

=> d ibib abs fhitrn hitrn retable

L36 ANSWER 1 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2001:833514 HCAPLUS
DOCUMENT NUMBER: 136:1609
TITLE: Production of adenine
with recombinant cells,
assays therefor
INVENTOR(S): Anderson, Christen M.;
William; Wiley, Sandra
Szabo, Tomas R.; Ghosh,
Pei, Yazhong; Carroll,
Mitokor, USA
PATENT ASSIGNEE(S):
SOURCE: PCT Int. Appl., 147 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

(ANT)
.ng
ger,
;
er H.;

Applicants

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001085944	A2	20011115	WO 2001-US15416	20010511
WO 2001085944	A3	20020829		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,			

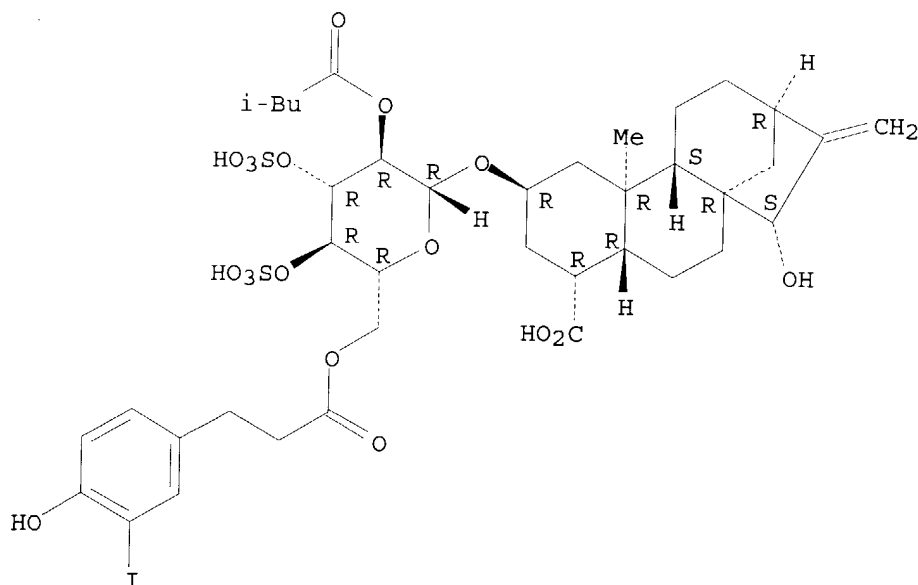
OTHER SOURCE(S) :

MARPAT 136:1609

IT 267886-33-9P

RN 267886-33-9 HCAPLUS

Absolute stereochemistry.



RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC

(Process)
(production of adenine nucleotide translocator (ANT) with recombinant cells, ANT ligands and screening assays therefor)

IT 267886-34-0 267886-55-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(production of adenine nucleotide translocator (ANT) with recombinant cells, ANT ligands and screening assays therefor)

IT 267886-39-5P 267886-48-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(production of adenine nucleotide translocator (ANT) with recombinant cells, ANT ligands and screening assays therefor)

IT 84882-67-7P 267886-17-9P 267886-18-0P
267886-19-1P 267886-21-5P 267886-32-8P
267886-36-2P 267886-38-4P 267886-40-8P
267886-41-9P 267886-42-0P 267886-43-1P
267886-44-2P 267886-45-3P 267886-46-4P
267886-47-5P 267886-49-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(production of adenine nucleotide translocator (ANT) with recombinant cells, ANT ligands and screening assays therefor)

=> d ibib abs fhitrn hitrn retable 2-17

L36 ANSWER 2 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2000:314834 HCAPLUS
DOCUMENT NUMBER: 132:344104
TITLE: Cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands
INVENTOR(S): Anderson, Christen M.; Davis, Robert E.; Clevenger, William; Wiley, Sandra Eileen; Miller, Scott W.; Szabo, Tomas R.; Ghosh, Soumitra S.
PATENT ASSIGNEE(S): Mitokor, USA
SOURCE: PCT I
CODEN
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

Applicants

PATENT NO.	KIND	NO.	DATE
WO 2000026370	A2	5883	19991103
WO 2000026370	A3	20001116	
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM		
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG		
EP 1049780	A1	20001108	EP 1999-968032 19991103
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO		
JP 2002539761	T2	20021126	JP 2000-579742 19991103
AU 769756	B2	20040205	AU 2000-24729 19991103

US 2001044144	A1	20011122	US 2001-811094	20010314
US 2002012992	A1	20020131	US 2001-810644	20010314
JP 2004154139	A2	20040603	JP 2003-408115	20031205
PRIORITY APPLN. INFO.:			US 1998-185904	A 19981103
			US 1999-393441	A 19990908
			JP 2000-579742	A3 19991103
			WO 1999-US25883	W 19991103

OTHER SOURCE(S): MARPAT 132:344104

AB Compns. and methods are provided for producing adenine nucleotide translocator (ANT) polypeptides and fusion proteins, including the production and use of recombinant expression constructs having a regulated promoter. Bacterial, insect, yeast (Sf9 cells and Trichoplusia ni cells), and mammalian expression systems are designed for reliable production of recombinant human ANT polypeptides in significant quantities, by employing regulated promoters and recombinant ANT fusion products with glutathione S-transferase and green fluorescent protein. The synthesis and properties of representative atractyloside derivs. as ANT ligands are described. ANT ligands and compns. and methods for identifying ANT ligands, agents that bind ANT, and agents that interact with ANT are also disclosed.

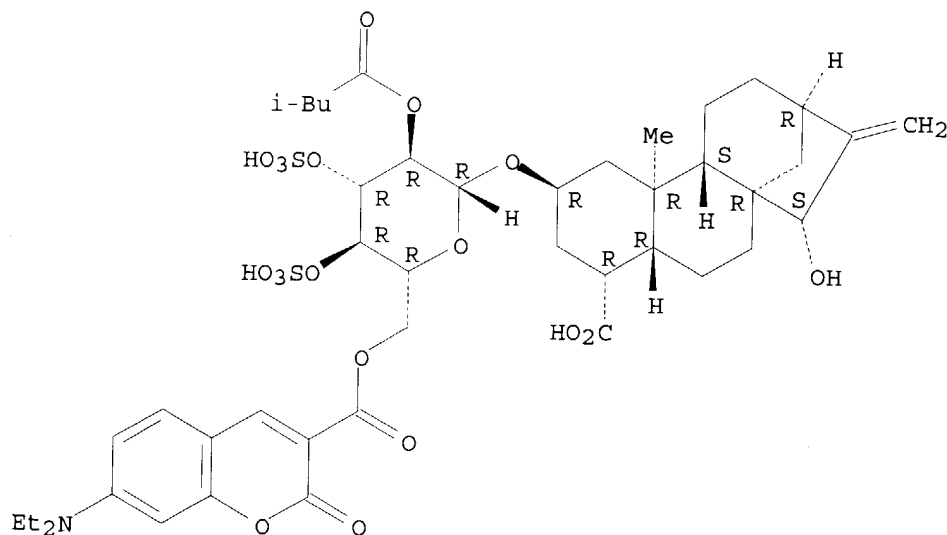
IT **267886-17-9P**

RL: ARG (Analytical reagent use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

RN 267886-17-9 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-[[7-(diethylamino)-2-oxo-2H-1-benzopyran-3-yl]carbonyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo-β-D-glucopyranosyl]oxy]-15-hydroxy-, (2β,4α,15α)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.

IT **267886-17-9P 267886-18-0P 267886-19-1P**

RL: ARG (Analytical reagent use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

- IT 267886-22-6P 267886-23-7P 267886-24-8P
 267886-25-9P 267886-26-0P 267886-27-1P
 267886-28-2P 267886-29-3P 267886-30-6P
 267886-31-7P 267886-50-0P 267886-51-1P
 267886-56-6P 267886-57-7P
 RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST
 (Analytical study); PREP (Preparation); USES (Uses)
 (cloning and production of human adenine nucleotide translocator and the
 synthesis and screening assays for novel ligands)
- IT 84882-67-7P 267886-32-8P 267886-33-9P
 267886-34-0P 267886-35-1P 267886-36-2P
 267886-37-3P 267886-38-4P 267886-39-5P
 267886-40-8P 267886-41-9P 267886-42-0P
 267886-43-1P 267886-44-2P 267886-45-3P
 267886-46-4P 267886-47-5P 267886-48-6P
 267886-49-7P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); SPN (Synthetic preparation); BIOL (Biological
 study); PREP (Preparation)
 (cloning and production of human adenine nucleotide translocator and the
 synthesis and screening assays for novel ligands)
- IT 267886-20-4P 267886-21-5DP, alkylidiamine derivs.
 267886-21-5P 267886-53-3P 267886-55-5P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (cloning and production of human adenine nucleotide translocator and the
 synthesis and screening assays for novel ligands)

L36 ANSWER 3 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 1982:595352 HCAPLUS

DOCUMENT NUMBER: 97:195352

TITLE: Synthesis of 6'-O-p-azidobenzoylratractoryloside, a short
 arm photoactivable derivative of atractoryloside.

AUTHOR(S): Studies of its binding and inhibitory properties
 Boulay. Francois; Lauquin, Guy J. M.; Vignais, Pierre
 V.

CORPORATE SOURCE: Lab. Biochim., CNRS/ERA, Grenoble, 38041, Fr.

SOURCE: FEBS Letters (1982), 143(2), 268-72

CODEN: FEBLAL; ISSN: 0014-5793

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The synthesis of a radiolabeled short-arm photoactivable derivative of
 atractoryloside (I), 6'-O-p-azido[14C]benzoylratractoryloside (II), is
 described, as well as its spectral properties and reversible binding to
 the ADP/ATP carrier protein in rat heart mitochondrial membrane. For the
 synthesis of II, p-amino[14C]benzoic acid was diazotized to give
 p-azido[14C]benzoic acid (III) which then was coupled to I following
 activation of the carboxyl group of III by N,N'-carbonyldiimidazole.
 Following removal of unreacted III, the residue was dissolved in MeOH and
 subjected to reversed-phase high-pressure liquid chromatog. in a
 µBondapak C18 column equipped with a CO-pell ODS guard column and
 isocratic elution with MeOH-NH4OAc-HOAc-H2O (58:1:1:40). The effluent
 contained a main product which was identified as II by mass spectrometry
 and whose purity was assessed by TLC. The absorption spectra of II and
 photolysis by UV irradiation were examined Reversible binding of II in the
 dark to the ADP/ATP carrier protein in the mitochondrial membrane and
 competitive inhibition of ADP transport in rat liver mitochondria by II
 indicated that II is recognized by the carrier with the same affinity and
 specificity as I itself.

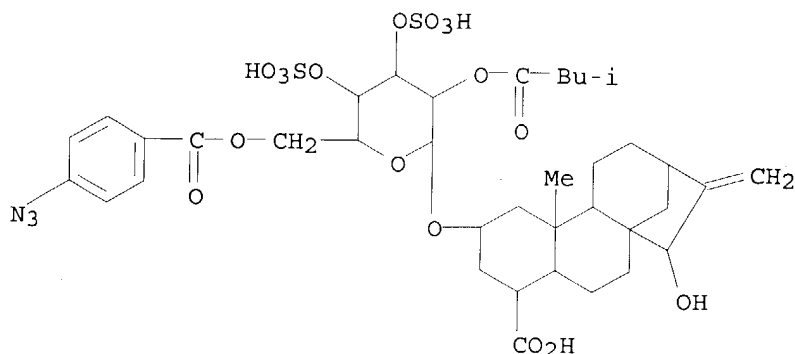
IT 83579-68-4P

RL: PRP (Properties); PREP (Preparation)

(preparation and properties of, binding to ADP/ATP carrier protein of heart mitochondria membrane in relation to)

RN 83579-68-4 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-(4-azidobenzoyl)-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo- β -D-glucopyranosyl]oxy]-15-hydroxy-, labeled with carbon-14, dipotassium salt, (2 β ,4 α ,15 α)-(9CI) (CA INDEX NAME)



● 2 K

IT 83579-68-4P

RL: PRP (Properties); PREP (Preparation)

(preparation and properties of, binding to ADP/ATP carrier protein of heart mitochondria membrane in relation to)

L36 ANSWER 4 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:465960 HCAPLUS

DOCUMENT NUMBER: 137:47439

TITLE: Preparation of amino acid derivatives for altering mitochondrial function and cellular responses

INVENTOR(S): Pei, Yazhong; Moos, Walter H.; Ghosh, Soumitra S.

PATENT ASSIGNEE(S): Mitokor, USA

SOURCE: PCT Int. Appl., 61 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002048092	A2	20020620	WO 2001-US48068	20011214
WO 2002048092	A3	20030109		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,

CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 AU 2002039595 A5 20020624 AU 2002-39595 20011214
 US 2002173543 A1 20021121 US 2001-20090 20011214
 US 6552076 B2 20030422
 PRIORITY APPLN. INFO.: US 2000-255803P P 20001215
 WO 2001-US48068 W 20011214

OTHER SOURCE(S): MARPAT 137:47439

AB Compds. R1COCHR2N(CH2CO2H)CO-A-C6H4NHCOR3 [A is a direct bond, (un)substituted alkylidiyl, -O-(alkylidiyl)-, -(alkylidiyl)-O-, -N(R')-(alkylidiyl)- (R' = H or alkyl), -(alkylidiyl)-N(R')-, heterocyclediyl, or heterocyclealkylidiyl; R1 = OH, alkoxy, aryloxy, arylalkyloxy, amino, or mono- or dialkylamino; R2 = H, (un)substituted alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclylalkyl; R3 = (un)substituted alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclylalkyl] were prepared for treating diseases by altering mitochondrial function that affects cellular processes. Thus, (HO2CCH2)2NCOC6H4NHAc-o was prepared by substitution reaction of glycine tert-Bu ester acetate with bromoacetate resin, reaction with 2-nitrobenzoic acid, nitro group reduction, acetylation with Ac2O, and resin cleavage using TFA. Biol. activities of compds. of the invention were examined in neuronal viability, displacement of an adenine nucleotide translocase ligand from isolated mitochondria, and chondrocyte cytoprotection assays.

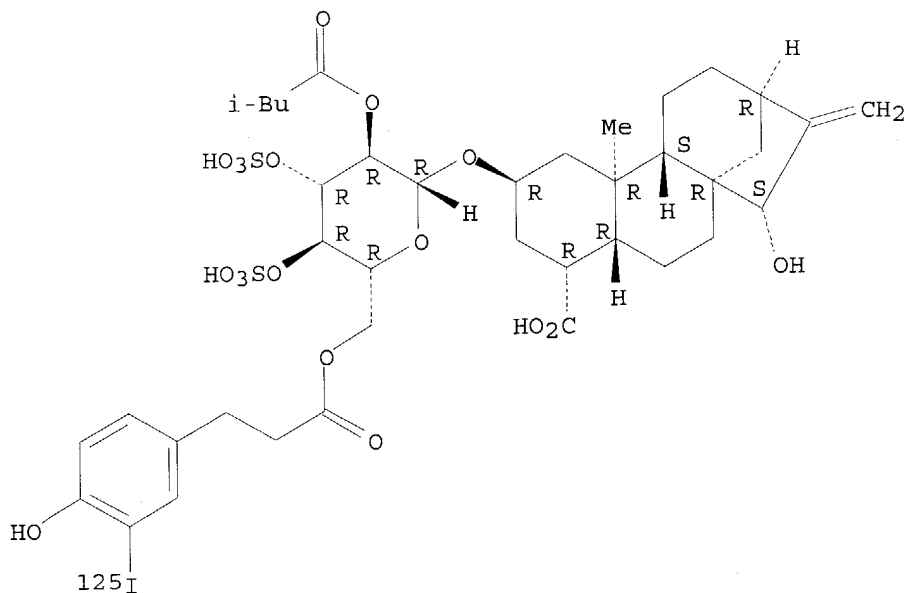
IT 437992-74-0

RL: BSU (Biological study, unclassified); BIOL (Biological study) (radioligand; measurement of binding efficacy of amino acid derivs. in relation to mitochondrial function and cellular responses)

RN 437992-74-0 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 15-hydroxy-2-[[6-O-[3-[4-hydroxy-3-(iodo-125I)phenyl]-1-oxopropyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo-β-D-glucopyranosyl]oxy]-, (2β,4α,15α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 437992-74-0

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(radioligand; measurement of binding efficacy of amino acid derivs. in
relation to mitochondrial function and cellular responses)

L36 ANSWER 5 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:686759 HCAPLUS

DOCUMENT NUMBER: 136:98644

TITLE: Fluorometric detection of ADP/ATP carrier deficiency
in human muscle

AUTHOR(S): Fiore, C.; Arlot-Guilligay, D.; Trezeguet, V.;
Lauquin, G. J.-M.; Brandolin, G.

CORPORATE SOURCE: Laboratoire de Biophysique et Biochimie des Systemes
Integres, CEA-Grenoble, UMR 5092 CEA-CNRS-UJF,
Grenoble, 38054, Fr.

SOURCE: Clinica Chimica Acta (2001), 311(2), 125-135

CODEN: CCATAR; ISSN: 0009-8981

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Defects in mitochondrial energy metabolism lead to severe disorders in humans referred to as mitochondriocytopathies. Most of them have been reported to result from deficiencies of one or more complexes of the respiratory chain and, more rarely, from mitochondrial transmembrane metabolite carrier defects. Dysfunctioning of the ADP/ATP carrier, which catalyzes the export of matrix ATP in exchange for cytosolic ADP, has been demonstrated to induce myopathies in mouse and in humans. To screen for ADP/ATP carrier deficiency in patients suffering from mitochondriocytopathy with no defined etiol., we have set up a fluorometric assay to quantify the ADP/ATP carrier in small muscle homogenates, without preliminary isolation of mitochondria. The assay is based on the use of a fluorescent derivative of atractyloside, namely naphthoyl-atractyloside, a highly specific inhibitor of ADP/ATP transport. Here, we describe anal. of healthy and pathol. muscle samples, and characterization of ADP/ATP carrier deficiencies in two patients, one displaying an absence of the carrier and the second one containing a limited amount of the carrier with altered binding properties.

IT 84882-67-7

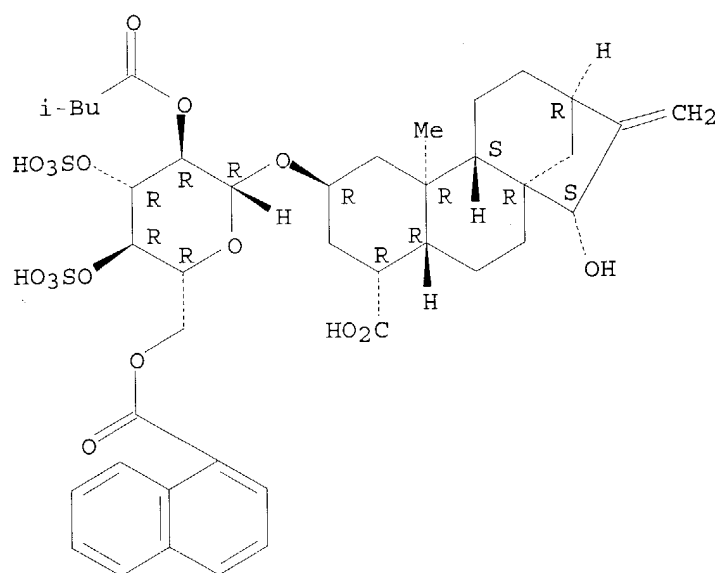
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
(Uses)

(fluorometric detection of ADP/ATP carrier deficiency in human muscle)

RN 84882-67-7 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 15-hydroxy-2-[[2-O-(3-methyl-1-oxobutyl)-6-O-(1-naphthalenylcarbonyl)-2,3-di-O-sulfo- β -D-glucopyranosyl]oxy]-,
(2 β ,4 α ,15 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 84882-67-7

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
(Uses)

(fluorometric detection of ADP/ATP carrier deficiency in human muscle)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Bakker, H	1993	16	548	J Inherited Metab Di	MEDLINE
Bakker, H	1993	342	175	Lancet	MEDLINE
Bakker, H	1993	33	412	Pediatr Res	MEDLINE
Bentlage, H	1995	1234	63	Biochim Biophys Acta	HCAPLUS
Block, M	1984	767	369	Biochim Biophys Acta	HCAPLUS
Boulay, F	1983	128	323	Anal Biochem	HCAPLUS
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Dolce, V	2001	98	2284	Proc Natl Acad Sci U	HCAPLUS
Esposito, L	1999	96	4820	Proc Natl Acad Sci U	HCAPLUS
Fiore, C	1998	80	137	Biochimie	HCAPLUS
Fiore, C	1999		143	Mitochondrial diseas	HCAPLUS
Graham, B	1997	16	226	Nat Genet	HCAPLUS
Huizing, M	1996	28	109	J Bioenerg Biomembr	HCAPLUS
Huizing, M	1998	30	277	J Bioenerg Biomembr	HCAPLUS
Huizing, M	1996	39	760	Pediatr Res	MEDLINE
Kaukonen, J	1999	65	256	Am J Hum Genet	HCAPLUS
Kaukonen, J	2000	289	782	Science	HCAPLUS
Klingenberg, M	1975	52	351	Eur J Biochem	HCAPLUS
Klingenberg, M	1978	65	456	Naturwissenschaften	HCAPLUS
Laemmli, U	1970	227	680	Nature	HCAPLUS
Leonard, J	2000	355	299	Lancet	MEDLINE
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Marty, I	1992	31	4058	Biochemistry	HCAPLUS
Moriyama, T	1971	246	3217	J Biol Chem	HCAPLUS
Munnich, A	1996	155	262	Eur J Pediatr	MEDLINE
Murphy, M	1989	977	123	Biochim Biophys Acta	HCAPLUS

Roux, P	1996	234	31	Anal Biochem	HCAPLUS
Rustin, P	1994	228	35	Clin Chim Acta	HCAPLUS
Schapira, A	1999	29	886	Eur J Clin Invest	HCAPLUS
Simon, D	1999	50	111	Annu Rev Med	HCAPLUS
Smeitink, J	1997	20	7	J Inherited Metab Di	
Towbin, H	1979	76	4350	Proc Natl Acad Sci U	HCAPLUS
Trijbels, J	1997	174	243	Mol Cell Biochem	
Vignais, P	1973	12	1508	Biochemistry	HCAPLUS
Wallace, D	2000	139	S70	Am Heart J	HCAPLUS
Wallace, D	1998	283	1482	Science	

L36 ANSWER 6 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:96368 HCAPLUS

DOCUMENT NUMBER: 124:225476

TITLE: Fluorometric titration of the mitochondrial ADP/ATP carrier protein in muscle homogenate with atractyloside derivatives

AUTHOR(S): Roux, Pierre; Le Saux, Agnes; Fiore, Christelle; Schwimmer, Christine; Dianoux, Anne-Christine; Trezeguet, Veronique; Vignais, Pierre V.; Lauquin, Guy J.-M.; Brandolin, Gerard

CORPORATE SOURCE: Laboratoire Biochimie, DBMS, Grenoble, 38054, Fr.

SOURCE: Analytical Biochemistry (1996), 234(1), 31-7

CODEN: ANBCA2; ISSN: 0003-2697

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors describe the chemical synthesis of the novel methylantraniloyl (Mant-) derivative of atractyloside (ATR), which is a specific inhibitor of the mitochondrial ADP/ATP carrier. The spectral properties of Mant-ATR and naphthoyl-ATR (N-ATR) are analyzed. Both derivs. bind to the membrane-bound ADP/ATP carrier at the same sites as ATR and carboxyatractyloside (CATR). When Mant-ATR and N-ATR are displaced by CATR, their fluorescence emissions are decreased and increased, resp. These fluorescence changes allow the titration of the CATR binding sites and therefore the quantitation of the amount of ADP/ATP carrier protein in a biol. preparation. The validity of the fluorometric titration was tested with

beef

heart mitochondria and confirmed by binding assays using radioactive ATR. The fluorometric method was applied to rabbit skeletal muscle homogenate and the results of titration were confirmed by binding assays of radioactive ATR. The reliability of the fluorometric method was assessed by comparing the amts. of CATR binding sites and the content of heme aa3 in muscle homogenates and in isolated mitochondria from the same homogenates. Because of its high sensitivity, the fluorometric titration of the ADP/ATP carrier requires small amts. of tissue. Mant-ATR and N-ATR can therefore be considered as convenient, reliable, and sensitive probes to quantify the amount of ADP/ATP carrier and detect a putative carrier protein deficiency in biopsy samples from human patients suffering from myopathies with no clear identified etiol.

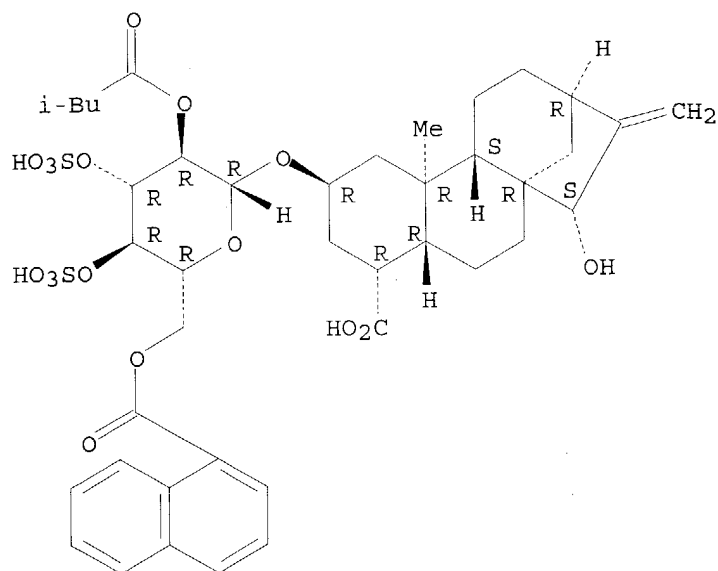
IT 84882-67-7

RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(fluorometry of mitochondrial ADP/ATP carrier in muscle with atractyloside derivs.)

RN 84882-67-7 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 15-hydroxy-2-[[2-O-(3-methyl-1-oxobutyl)-6-O-(1-naphthalenylcarbonyl)-2,3-di-O-sulfo-β-D-glucopyranosyl]oxy]-, (2β,4α,15α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 84882-67-7

RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(fluorometry of mitochondrial ADP/ATP carrier in muscle with atractyloside derivs.)

IT 174584-83-9P

RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(fluorometry of mitochondrial ADP/ATP carrier in muscle with atractyloside derivs.)

L36 ANSWER 7 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1986:530300 HCAPLUS

DOCUMENT NUMBER: 105:130300

TITLE: Fluorescent probes of the mitochondrial ADP/ATP carrier protein

AUTHOR(S): Block, Marc R.; Boulay, Francois; Brandolin, Gerard; Dupont, Yves; Lauquin, Guy J. M.; Vignais, Pierre V.
CORPORATE SOURCE: Dep. Rech. Fundamen., Cent. Etudes Nucl., Grenoble, 38041, Fr.

SOURCE: Methods in Enzymology (1986), 125 (Biomembranes, Pt. M), 639-49
CODEN: MENZAU; ISSN: 0076-6879

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Fluorescent probes of the ADP/ATP-carrier protein (I) include naphthoyl-ADP and naphthoyl-ATP, and atractyloside (ATR) derivs., dansyl-ATR, dansyl-4-aminobutyryl-ATR and naphthoyl-ATR. The preparation and use of these compds. in the determination and conformational anal. of I are described.

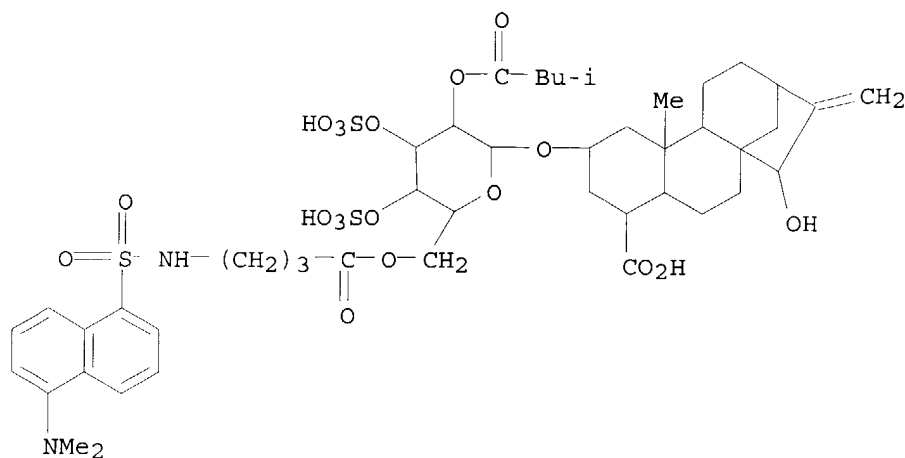
IT 84872-88-8

RL: ANST (Analytical study)

(as fluorescent probe, of adenine nucleotide-transporting protein)

RN 84872-88-8 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-[4-[[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]amino]-1-oxobutyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo-β-D-glucopyranosyl]oxy]-15-hydroxy-,
(2β,4α,15α)- (9CI) (CA INDEX NAME)



IT 84872-88-8 84882-67-7

RL: ANST (Analytical study)

(as fluorescent probe, of adenine nucleotide-transporting protein)

L36 ANSWER 8 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1983:139309 HCAPLUS

DOCUMENT NUMBER: 98:139309

TITLE: Binding of spin-labeled carboxyatractylate to mitochondrial adenosine 5'-diphosphate/adenosine 5'-triphosphate carrier as studied by electron spin resonance

AUTHOR(S): Munding, Anton; Beyer, Klaus; Klingenberg, Martin

CORPORATE SOURCE: Inst. Physiol. Chem., Univ. Muenchen, Munich, 8000/2, Fed. Rep. Ger.

SOURCE: Biochemistry (1983), 22(8), 1941-7

CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The spin-label 2,2,5,5-tetramethyl-1-oxy-3-pyrroline-3-carboxylic acid was attached to the inhibitor carboxyatractylate of the mitochondrial ADP/ATP carrier (adenine nucleotide translocase). Being closely linked to the inhibitor, the spin-label should reflect the mobility of the carboxyatractylate. When bound to the carrier in mitochondria, spin-labeled carboxyatractylate reveals a most unusual hyperfine splitting of 72 G. A 2nd spectral component with a hyperfine splitting of 62 G is also mainly due to carrier-bound inhibitor. A similar spectrum with somewhat reduced hyperfine splitting was observed with the detergent-solubilized protein, whereas reincorporation into phospholipid membranes yielded almost the same spectra as in mitochondria. The carrier-bound spin-label is concluded to be highly immobilized. The less immobilized spectral component is discussed in terms of strongly anisotropic label motion. In addition, the unusual splitting is interpreted to indicate the highly polar environment of the nitroxide. The interpretations are supported by the temperature dependence, which indicates a

reversible progressive spin-label mobilization up to 50°.
Membrane-impermeable reducing agents showed that the spin-label is easily accessible from the aqueous phase.

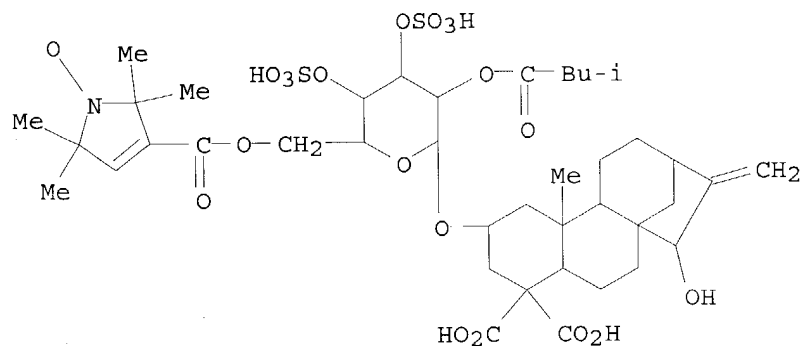
IT **84602-22-2**

RL: PROC (Process)

(adenine nucleotide translocase binding of)

RN 84602-22-2 HCAPLUS

CN Kaur-16-ene-18,19-dioic acid, 1-[[6-O-[(2,5-dihydro-2,2,5,5-tetramethyl-1-oxy-1H-pyrrol-3-yl)carbonyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo-β-D-glucopyranosyl]oxy]-15-hydroxy-, (2β,15α)- (9CI) (CA
INDEX NAME)



IT **84602-22-2**

RL: PROC (Process)

(adenine nucleotide translocase binding of)

L36 ANSWER 9 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1983:49494 HCAPLUS

DOCUMENT NUMBER: 98:49494

TITLE: Photolabeling approach to the study of the topography of the atractyloside binding site in mitochondrial adenosine 5'-diphosphate/adenosine 5'-triphosphate carrier protein

AUTHOR(S): Boulay, Francois; Lauquin, Guy J. M.; Tsugita, Akira; Vignais, Pierre V.

CORPORATE SOURCE: Dep. Rech. Fondam., Cent. Etud. Nucl., Grenoble, Fr.

SOURCE: Biochemistry (1983), 22(2), 477-84

CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The binding site of atractyloside (I), an impermeant inhibitor of the mitochondrial ADP/ATP carrier protein (adenine nucleotide translocase) (II), was investigated by photolabeling techniques. The photolabels used were long- and short-arm radioactive derivs. of I, namely, 6'-O-[3-[N-(4-azido-2-nitrophenyl)amino]propionyl]-I, 6'-O-[4-[N-(4-azido-2-nitrophenyl)amino]butyryl]-I, and 6'-O-(p-azidobenzoyl)-I. The photolabeling step was carried out with bovine heart mitochondria. Covalently photolabeled II was extracted by Triton X-100 and further purified by hydroxylapatite chromatog., acetone precipitation, and washing with a mixture of

formic acid, EtOH, and ether. The peptide chain was cleaved at methionine and cysteine residues by specific chemical reagents. Cleavage of II (mol. weight 32,000) at the methionine residues by CNBr yielded a large, 23,000-dalton segment, called CB1, that was radiolabeled and a number of unlabeled small fragments. Cleavage at cysteinyl residues by cyanide at

alkaline pH involved the prior reaction of SH groups with 5,5'-dithiobis(2-nitrobenzoic acid). Cyanide cleavage of the CB1 fragment, which contains 3 cysteinyl residues, resulted in the accumulation of a number of overlapping peptides and 4 nonoverlapping peptides, these latter being referred to as CN peptides. With both the long- and short-arm azido-I derivs. used, essentially only 1 of the CN peptides, with a mol. weight of .apprx.4500, was found to be photolabeled; this peptide was situated at the C-terminus of the CB1 fragment between cysteine-159 and methionine-200. Thus, the I site in membrane-bound II is located near the center of mol.; this region may be exposed to the cytosolic side of the inner mitochondrial membrane.

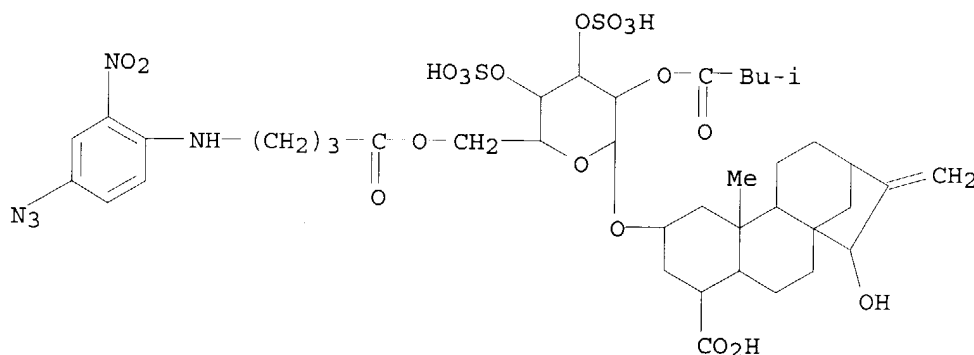
IT 65792-55-4

RL: BIOL (Biological study)

(adenine nucleotide translocase photolabeling by, atractyloside-binding site in relation to)

RN 65792-55-4 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 2-[[[6-O-[4-[(4-azido-2-nitrophenyl)amino]-1-oxobutyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo-β-D-glucopyranosyl]oxy]-15-hydroxy-, dipotassium salt, (2β,4α,15α) - (9CI) (CA INDEX NAME)



● 2 K

IT 65792-55-4 83876-80-6 83876-82-8

RL: BIOL (Biological study)

(adenine nucleotide translocase photolabeling by, atractyloside-binding site in relation to)

L36 ANSWER 10 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1983:103893 HCAPLUS

DOCUMENT NUMBER: 98:103893

TITLE: Synthesis and properties of fluorescent derivatives of atractyloside as potential probes of the mitochondrial ADP/ATP carrier protein

AUTHOR(S): Boulay, Francois; Brandolin, Gerard; Lauquin, Guy J. M.; Vignais, Pierre V.

CORPORATE SOURCE: Dep. Rech. Fondam., Cent. Etudes Nucl., Grenoble, 38041, Fr.

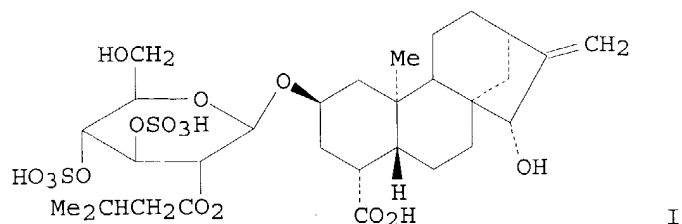
SOURCE: Analytical Biochemistry (1983), 128(2), 323-30

CODEN: ANBCA2; ISSN: 0003-2697

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB The chemical synthesis of fluorescent derivs. of atractyloside (I) (ATR), an inhibitor of the mitochondrial ADP/ATP carrier protein, is described. These derivs. are: 6'-O-dansyl-ATR; 6'-O-dansyl-aminobutyryl-ATR; and 6'-O-naphthoyl-ATR. The spectral properties of these analogs were analyzed, and their biol. features were compared to those of ATR. The fluorescence emission of the dansyl-ATR derivs. was increased in organic solvents and that of naphthoyl-ATR was decreased; for both analogs, solubilization in organic solvents resulted in a blue shift of the emission peak. The fluorescent dansyl- and naphthoyl-ATR derivs. were specifically recognized by the mitochondrial ADP/ATP carrier protein. Because of their spectral properties and their biochem. reactivities, the fluorescent analogs of ATR can be considered as potential probes to investigate the topog. of the ADP/ATP carrier in the mitochondrial membrane and to monitor conformational changes of the ADP/ATP carrier protein associated with transport.

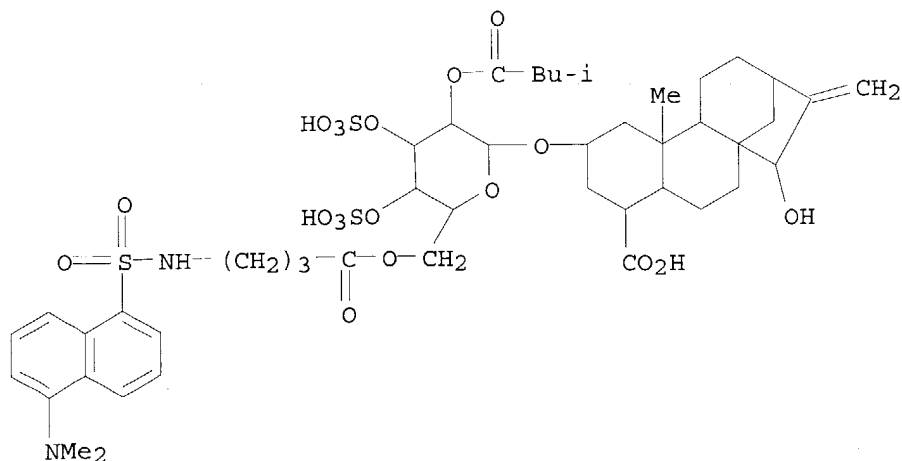
IT **84872-88-8P**

RL: PREP (Preparation)

(preparation of, as mitochondrial ADP/ATP carrier protein probe)

RN 84872-88-8 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-[4-[[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]amino]-1-oxobutyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo-β-D-glucopyranosyl]oxy]-15-hydroxy-, (2β,4α,15α)- (9CI) (CA INDEX NAME)



IT **84872-88-8P 84882-67-7P**

RL: PREP (Preparation)

(preparation of, as mitochondrial ADP/ATP carrier protein probe)

L36 ANSWER 11 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1982:577110 HCAPLUS

DOCUMENT NUMBER: 97:177110

TITLE: Interaction of naphthoyl-ADP a fluorescent ADP analog, with the ADP/ATP carrier protein in the mitochondrial membrane

AUTHOR(S): Block, Marc R.; Lauquin, Guy J. M.; Vignais, Pierre V.

CORPORATE SOURCE: Fac. Med., CEN/Grenoble, Grenoble, 38041, Fr.

SOURCE: Biochemistry (1982), 21(22), 5451-7

CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 3'-O-(1-Naphthoyl ADP (N-ADP), a fluorescent analog of ADP, was established as a potent inhibitor of ADP/ATP transport in mitochondria and inside-out sonic particles; the K_i value was $\approx 5 \mu\text{M}$. The inhibition was of a mixed type. On the other hand, N-ADP was not transported in a measurable way in either type of particles. Upon binding to the particles, the fluorescent intensity of N-ADP was decreased; the release of the bound N-ADP upon addition of carboxyatractyloside (CATR) to mitochondria and bongkreikic acid (BA) to sonic particles was reflected by increases of fluorescence. In parallel assays specifically bound $[^{14}\text{C}]\text{N-ADP}$ was equated to $[^{14}\text{C}]\text{N-ADP}$ released upon addition of either CATR (mitochondria) or BA (sonic particles). The specific binding of N-ADP corresponded to 1.4-1.6 nmol/mg of protein in mitochondria, with a K_d value of $3 \mu\text{M}$, and to 1.5-1.6 nmol/mg of protein in sonic particles, with a K_d value of $6 \mu\text{M}$. Similar values were obtained for N-ATP binding. These values are at least twice as high as those found for specific ADP or ATP binding, suggesting that N-ADP or N-ATP binds to potential nucleotide binding sites that were not totally occupied by ADP or ATP. Whereas nearly all the specifically bound N-ADP in mitochondria was displaced by an excess of ADP ($400 \mu\text{M}$) at pH 7.4, only 30% could be removed from sonic particles under the same conditions. Further at pH 6.5, $\leq 1/2$ of the specifically bound N-ADP could be removed by excess ADP in mitochondria and only 10-20% in sonic particles. These results indicate that each ADP/ATP carrier unit contains ≥ 2 types of nucleotide sites capable of interacting with N-ADP. Because of the hydrophobic nature of the naphthoyl moiety of N-ADP, the data suggest that differences in N-ADP binding in mitochondria and sonic particles are related to differences in the hydrophobic nature of their sites. Inactivation studies were carried out with mitochondria and sonic particles to compare the sensitivity to UV light and butanedione of the binding of N-ADP, $[^3\text{H}]\text{BA}$, and $[^{14}\text{C}]\text{Ac-CATR}$, a radiolabeled substitute for CATR. Both in mitochondria and in sonic particles, UV light and butanedione more rapidly inactivated the binding of N-ADP than that of $[^3\text{H}]\text{BA}$. However, in mitochondria, UV light more rapidly inactivated the binding of $[^{14}\text{C}]\text{Ac-CATR}$ than that of N-ADP; the reverse was true for the inactivation by butanedione. The inactivation data conclusively indicate that BA, CATR, and adenine nucleotides are recognized by different specific sets of amino acids.

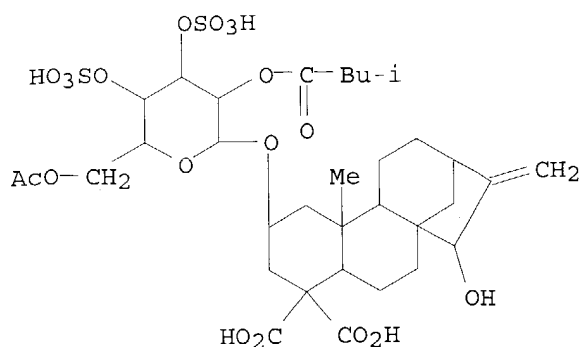
IT 83103-09-7

RL: BIOL (Biological study)

(adenine nucleotide transporter of mitochondria binding of, naphthoyl-ADP in comparison with)

RN 83103-09-7 HCAPLUS

CN Kaur-16-ene-18,19-dioic acid, 2-[[6-O-acetyl-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo- β -D-glucopyranosyl]oxy]-15-hydroxy-, dipotassium salt, (2 β ,15 α)- (9CI) (CA INDEX NAME)



● 2 K

IT 83103-09-7

RL: BIOL (Biological study)
(adenine nucleotide transporter of mitochondria binding of,
naphthoyl-ADP in comparison with)

L36 ANSWER 12 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1980:581175 HCAPLUS

DOCUMENT NUMBER: 93:181175

TITLE: Chemical radiolabeling of carboxyatractyloside by
[14C]-acetic anhydride. Binding properties of
[14C]-acetylcarboxyatractyloside to the mitochondrial
ADP/ATP carrier

AUTHOR(S): Block, Marc R.; Pougeois, Richard; Vignais, Pierre V.

CORPORATE SOURCE: Dep. Rech. Fondamentale, CEN, Grenoble, 38041, Fr.

SOURCE: FEBS Letters (1980), 117(1), 335-40

CODEN: FEBLAL; ISSN: 0014-5793

DOCUMENT TYPE: Journal

LANGUAGE: English

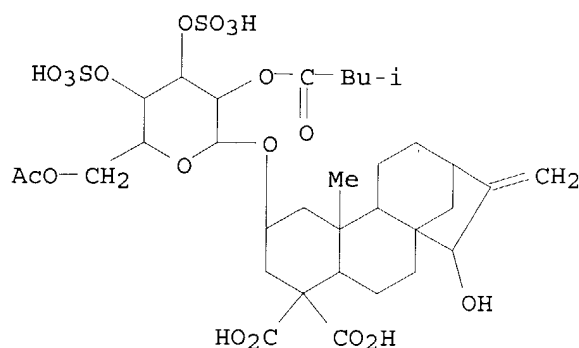
AB [14C]acetylcarboxyatractyloside (I) was virtually identical to
carboxyatractyloside (CAT) in binding to the mitochondrial ADP/ATP
carrier. I bound to specific sites of the outer membrane of the carrier
with an affinity constant (Kd) of 2-10 μ M and irreversibly inhibited
ADP/ATP transport. I was replaced by CAT but not by atractyloside and the
I-carrier complex was stable after solubilization. I, in double-labeling
expts. with [3H]bongkreikic acid (BA), showed mutual exclusion of CAT and
BA mitochondrial binding sites. This exclusion was dependent on exptl.
conditions. Further, addition of ADP + I during the pre-labeling step
resulted in a much lower release of I on BA addition than when ADP + BA were
added during the displacement step. This is probably related to different
conformations of the carrier. A preparative method for I is given.

IT 75240-94-7

RL: BIOL (Biological study)
(mitochondrial ADP-ATP carrier binding and inhibition by)

RN 75240-94-7 HCAPLUS

CN Kaur-16-ene-18,19-dioic acid, 2-[[6-O-acetyl-2-O-(3-methyl-1-oxobutyl)-3,4-
di-O-sulfo- β -D-glucopyranosyl]oxy]-15-hydroxy-, (2 β ,15 α)-
(9CI) (CA INDEX NAME)



IT 75240-94-7

RL: BIOL (Biological study)
(mitochondrial ADP-ATP carrier binding and inhibition by)

IT 75240-95-8P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

L36 ANSWER 13 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1980:123624 HCAPLUS

DOCUMENT NUMBER: 92:123624

TITLE: Fragmentation of the ADP/ATP carrier protein from beef heart mitochondria. Localization of the atractyloside binding site in a peptide obtained by cyanogen bromide cleavage

AUTHOR(S): Boulay, Francois; Lauquin, Guy J. M.; Vignais, Pierre V.

CORPORATE SOURCE: Dep. Rech. Fondam., CEN, Grenoble, 38041, Fr.

SOURCE: FEBS Letters (1979), 108(2), 390-4

CODEN: FEBLAL; ISSN: 0014-5793

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The atractyloside bind site of the ATP/ADP carrier protein of beef heart mitochondria was localized by photolabeling intact mitochondria with the nonpenetrant inhibitor N-4-azido-2-nitrophenylaminobutyryl atractyloside-3H (I), followed by extraction and purification of the photolabeled

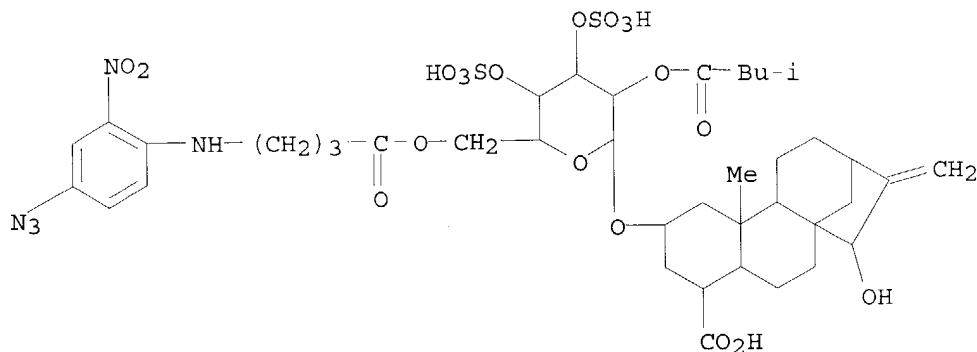
carrier and identification of the 3H-labeled peptide moiety following CNBr cleavage. CNBr cleavage products of the labeled purified protein were separated by column chromatog. and Na dodecyl sulfate-polyacrylamide gel electrophoresis. The 3H-labeled product consisted of a single 23,000-mol.-weight product which was homogeneous on gel electrophoresis. Amino acid anal. showed the polarity index of this product to be the same as that of the intact carrier (40%) and that the fragment and the intact carrier have the same blocked N-terminal amino acid residue in common. As I does not penetrate the mitochondrial membrane, at least part of the 23,000-mol.-weight fragment corresponds to the outer domain of the carrier protein and ≥1 region of this domain constitutes the atractyloside binding site. This domain is, hence, on the cytosol-exposed surface in the mitochondrial membrane. Studies with arylazido ADP indicated that ADP and atractyloside may bind to closely related sites on the carrier.

IT 73062-49-4

RL: BIOL (Biological study)
(adenine nucleotide carrier binding site for, of mitochondrial membrane)

RN 73062-49-4 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-[4-[(4-azido-2-nitrophenyl)amino]-1-oxobutyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo- β -D-glucopyranosyl]oxy]-15-hydroxy-, (2 β ,4 α ,15 α)- (9CI) (CA INDEX NAME)



IT 73062-49-4

RL: BIOL (Biological study)
(adenine nucleotide carrier binding site for, of mitochondrial membrane)

L36 ANSWER 14 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1978:100435 HCAPLUS

DOCUMENT NUMBER: 88:100435

TITLE: Photoaffinity labeling of the adenine nucleotide carrier in heart and yeast mitochondria by an arylazido ADP analog

AUTHOR(S): Lauquin, Guy J. M.; Brandolin, Gerard; Lunardi, Joel; Vignais, Pierre V.

CORPORATE SOURCE: Dep. Rech. Fondam., CEN, Grenoble, Fr.

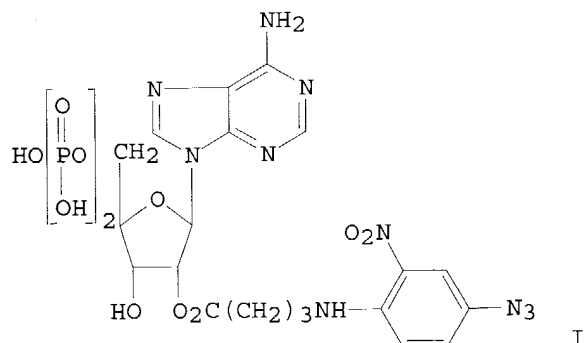
SOURCE: Biochimica et Biophysica Acta (1978), 501(1), 10-19

CODEN: BBACAQ; ISSN: 0006-3002

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB Arylazido analogs of ADP and ATP (N-4-azido-2-nitrophenylaminobutyryl-ADP (I) and N-4-azido-2-nitrophenylaminobutyryl-ATP) were prepared in radioactive form and used in photolabeling expts. to identify the adenine

nucleotide carrier in mitochondria and sonic submitochondrial particles. When added in the dark to beef heart mitochondria, I bound to the adenine nucleotide carrier. I was not transported across the membrane to the matrix space, but did inhibit ADP transport in mitochondria. The inhibition was of a mixed type with a K_i value of .apprx. 10 μ M. The nitrene derivative formed on photoirradn. of tritiated I bound to a polypeptide of apparent mol. weight 30,000 in beef heart mitochondria and 37,000 in *Saccharomyces cerevisiae* mitochondria. Photolabeling was prevented by preincubation of the mitochondria with atractyloside or carboxyatractyloside. Photoirradn. of sonic submitochondrial particles from beef heart (inside-out particles) with tritiated I resulted in the labeling of the 30,000-dalton polypeptide and also in the labeling of higher-mol.-weight peptides (50,000-55,000) probably belonging to F1-ATPase. Addition of bongkrekic acid specifically decreased the photolabeling of the 30,000-dalton polypeptide. An arylazido derivative of atractyloside (N-4-azido-2-nitrophenylaminobutyl-atractyloside) bound on photoirradn. to the 30,000-dalton polypeptide in beef heart mitochondria and to the 37,000-dalton polypeptide in *S. cerevisiae* mitochondria. Since the adenine nucleotide carrier is readily damaged by UV light, nitroarylazido analogs of ADP and ATP or of atractyloside, which are photoactivated in visible light, were used in preference to other azido analogs, which require UV light for photoactivation. Thus, the same mitochondrial protein belonging to the adenine nucleotide transport system is able to bind ADP (or ATP) and atractyloside.

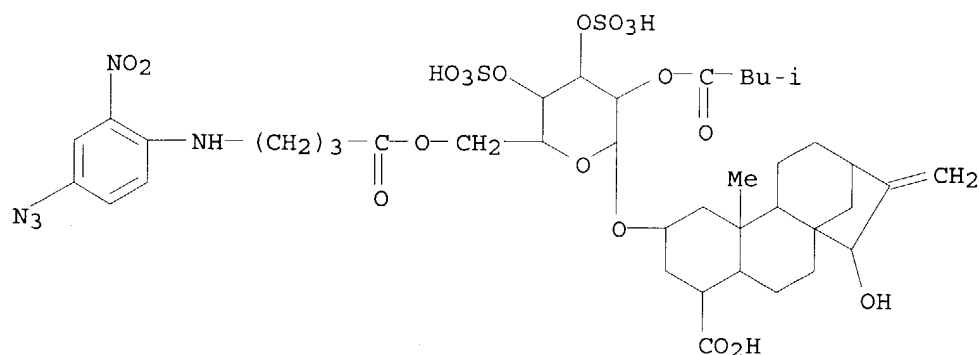
IT 65792-55-4

RL: BIOL (Biological study)

(photoaffinity labeling of adenine nucleotide carrier of mitochondria by)

RN 65792-55-4 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-[4-[(4-azido-2-nitrophenyl)amino]-1-oxobutyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo- β -D-glucopyranosyl]oxy]-15-hydroxy-, dipotassium salt, (2 β ,4 α ,15 α)-(9CI) (CA INDEX NAME)



● 2 K

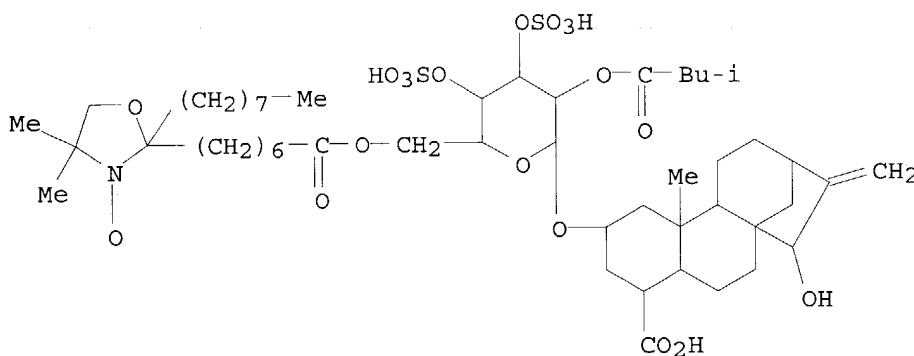
IT 65792-55-4

RL: BIOL (Biological study)

(photoaffinity labeling of adenine nucleotide carrier of mitochondria by)

L36 ANSWER 15 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1977:166506 HCAPLUS
 DOCUMENT NUMBER: 86:166506
 TITLE: Spin-labeled acyl atractyloside as a probe of the mitochondrial adenosine diphosphate carrier. Asymmetry of the carrier and direct lipid environment
 AUTHOR(S): Lauquin, Guy J. M.; Devaux, Philippe F.; Bienvenue, Alain; Villiers, Christian; Vignais, Pierre V.
 CORPORATE SOURCE: Dep. Rech. Fondam., CEN, Grenoble, Fr.
 SOURCE: Biochemistry (1977), 16(6), 1202-8
 CODEN: BICHAW; ISSN: 0006-2960
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB A number of spin-labeled acyl derivs. of atractyloside, (m,n)acyl-ATR (general formula: $\text{CH}_3(\text{CH}_2)_m\text{CX}(\text{CH}_2)_n\text{COO-ATR}$, where X is an oxazolidine ring containing a nitroxide), were synthesized and used to probe the ADP carrier in heart mitochondria. They inhibit ADP transport with the same efficiency as unlabeled acyl-ATRs. The inhibition is a mixed competitive and noncompetitive inhibition. The long chain acyl-ATRs ((10,3)-, (7,6)-, (7,8)-, and (5,10)acyl-ATRs) and also the short chain (0,2)acyl-ATR, when added at low concns. to heart mitochondria, give rise to more immobilized ESR spectra than when added to liposomes. On addition of atractyloside or of other specific ligands, spin-labeled long-chain acyl-ATRs bound to the ADP carrier are displaced from their binding site toward the lipid phase of the mitochondrial membrane and the short chain (0,2)acyl-ATR is released into the aqueous phase. Spin-labeled long-chain acyl-ATRs do not show any evidence of binding to a protein when incubated with inside out submitochondrial particles, in spite of the fact that these particles are able to transport ADP. These results are discussed with respect to the size and the asymmetry of the ADP carrier in the mitochondrial membrane and the mechanism of ADP transport.
 IT 63193-89-5
 RL: BIOL (Biological study)
 (as mitochondrial membrane probe)
 RN 63193-89-5 HCAPLUS
 CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-[7-(4,4-dimethyl-2-octyl-3-oxy-2-oxazolidinyl)-1-oxoheptyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo- β -D-glucopyranosyl]oxy]-15-hydroxy-, dipotassium salt, (2 β ,4 α ,15 α)-(9CI) (CA INDEX NAME)



● 2 K

IT 63193-89-5 63193-90-8 63193-91-9

63193-92-0 63193-93-1 63196-04-3

RL: BIOL (Biological study)
(as mitochondrial membrane probe)

L36 ANSWER 16 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1976:572971 HCAPLUS

DOCUMENT NUMBER: 85:172971

TITLE: Aryl-azido atractylosides as photoaffinity labels for
the mitochondrial adenine nucleotide carrier

AUTHOR(S): Lauquin, Guy; Brandolin, Gerard; Vignais, Pierre

CORPORATE SOURCE: Dep. Rech. Fondam./Biochim., CEN, Grenoble, Fr.

SOURCE: FEBS Letters (1976), 67(3), 306-11

CODEN: FEBLAL; ISSN: 0014-5793

DOCUMENT TYPE: Journal

LANGUAGE: English

GI For diagram(s), see printed CA Issue.

AB A photoactive arylazido derivative of atractyloside was used to label covalently the ADP carrier in rat heart mitochondria. The synthesis of 6' [4N(4-azido-2-nitrophenyl)amino]butyryl-*atractyloside* (I) and its propionyl analog is described. I competitively inhibits ADP transport with the same efficiency as *atractyloside* and competes with *atractyloside* for binding to mitochondria. The nitrene derivative formed on irradiation of I binds covalently to mitochondria. By this means, the ADP carrier protein was characterized by Na dodecyl sulfate-polyacrylamide gel electrophoresis; its mol. weight is .apprx.30,000.

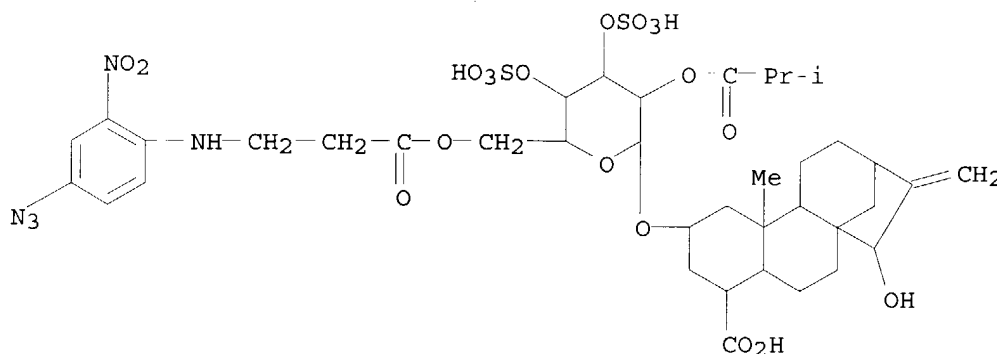
IT 60792-98-5

RL: BIOL (Biological study)

(ADP carrier protein binding and photolabeling by)

RN 60792-98-5 HCAPLUS

CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-[3-[(4-azido-2-nitrophenyl)amino]-1-oxopropyl]-2-O-(2-methyl-1-oxopropyl)-3,4-di-O-sulfo- β -D-glucopyranosyl]oxy]-15-hydroxy-, dipotassium salt,
(2 β ,4 α ,15 α)-(9CI) (CA INDEX NAME)



● 2 K

IT 60792-98-5 60792-99-6

RL: BIOL (Biological study)

(ADP carrier protein binding and photolabeling by)

L36 ANSWER 17 OF 46 HCAPLUS COPYRIGHT 2004 ACS on STN

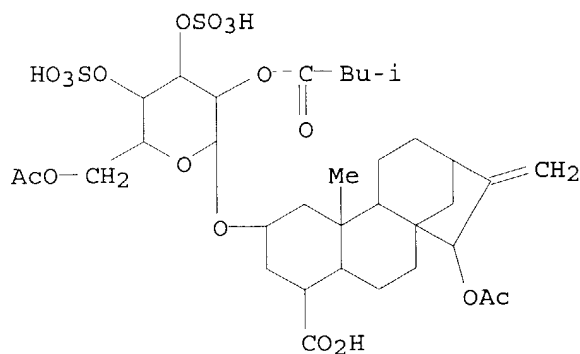
ACCESSION NUMBER: 1967:517201 HCAPLUS

DOCUMENT NUMBER: 67:117201
 TITLE: Structure of atractyloside
 AUTHOR(S): Piozzi, Franco; Quilico, Adolfo; Fuganti, Claudio; Ajello, Tommaso; Sprio, Vincenzo
 CORPORATE SOURCE: Univ. Palermo, Palermo, Italy
 SOURCE: Gazzetta Chimica Italiana (1967), 97(6), 935-54
 CODEN: GCITA9; ISSN: 0016-5603
 DOCUMENT TYPE: Journal
 LANGUAGE: Italian

GI For diagram(s), see printed CA Issue.

AB A structure is assigned to the title compound (I), m. 157-8° (decomposition) $[\alpha]_D^{25} -53^\circ$ (c 1.1, H₂O), is obtained from *Atractylis gummifera* roots according to known procedures. I (3.07 g.) in a mixture of 100 ml. water and 200 ml. EtOH is hydrogenated in the presence of 200 ml. 10% Pd/C to give dihydroatractyloside, m. 172-3°, $[\alpha]_D^{25} -34.5^\circ$ (c 1.0, H₂O). A mixture of 300 ml. M H₃PO₄ and 1.606 g. I is heated to give isovaleric acid. A solution of 200 mg. I in M H₂SO₄ is refluxed 4 hrs. to give D-glucose (II). A solution of 1.6 g. I in 20 ml. 20% KOH is refluxed 8 hrs., diluted with 80 ml. water, cooled, and acidified with 10% HCl to give atractyligenin (III), m. 180°. Similarly prepared is hydroatractyligenin, m. 236-7° (EtOAc). A solution of 1 g. I in 5 ml. pyridine and 5 ml. Ac₂O is kept 24 hrs. to give di-O-acetylpatractyloside (IV). A solution of 2 g. I in 40 ml. water containing 2 g. Ba(OH)₂ is heated to give apo-atractyloside (V) Ba salt, m. 155° (decomposition), which is converted to V di-K salt, m. 232-4°. A mixture of 3 g. V Ba salt, 100 g. 1% Na amalgam, 20 ml. water, and 80 ml. MeOH is agitated 72 hrs. and the product is treated with CH₂N₂ to give penta-O-acetylpatractyline Me ester (VI), m. 165-7° (EtOH). A mixture of 2 g. of I, 2 ml. concentrated HCl, and 200 ml. MeOH is kept 24 hrs. and the product is treated with CH₂N₂ to give isovalerylpatractyline Me ester (VII), m. 112-14°. A mixture of 200 ml. VII, 20 ml. 5% Ba(OH)₂, and 20 ml. MeOH is heated 10 min. at 70-80°, CO₂ is introduced into the mixture, and the product is treated with CH₂N₂ to give atractyline Me ester (VIII), m. 130-2°; VII is treated with Ac₂O and pyridine to give VI m. 165-7° (EtOH). A mixture of 800 ml. IV, 0.8 ml. concentrated HCl, and 80 ml. MeOH is kept 24 hrs. and the product is treated with CH₂N₂ to give di-O-acetylisovalerylpatractyline Me ester (IX), m. 108°. A mixture of 100 ml. VIII and 5 ml. 20% KOH is refluxed 6 hrs. to give III; a mixture 100 ml. VIII and 5 ml. M H₂SO₄ is refluxed 4 hrs. to give II. I, V di-K salt, V Ba salt, VII, atractyline Me ester, and VI give neg. Fehling tests. A solution of 1 g. hydroatractyloside in EtOH is treated with CH₂N₂, the EtOH is removed, the product is dissolved in 20 ml. HOAc, a solution prepared from 200 ml. CrO₃, 5 ml. HOAc, and 0.1 ml. water is added in about 10 min., and the mixture is refluxed with 100 ml. 20% KOH to give about 20% 15-oxohydroatractyligenin Me ester, m. 124°; monoacetyl derivative m. 159°. Results for the HIO₄ titration of I, V di-K salt, atractyline Me ester, VII, X, Me α -D-glucopyranoside and Me 4,6-O-benzylidene- α -D-glucopyranoside are given. A solution of 5 g. I and 25 ml. HCONMe₂ is treated with 5 g. Ag₂O and 10 ml. MeI, the mixture is agitated 24 hrs. and added to 200 ml. MeOH, the mixture is evaporated to dryness, and 200 ml. 2N H₂SO₄ is added. The mixture is refluxed 12 hrs., BaCO₃ is added at 40-50°, and the product is treated with 5 ml. Ac₂O and 5 ml. pyridine to give about 600 ml. product. Gas phase chromatog. shows that the product contains 1,2,3,4,6-penta-O-acetyl-D-glucose, 3-O-methyl-1,2,4,6-tetra-O-acetyl-D-glucose, 2-O-methyl-1,3,4,6-tetra-O-acetyl-D-glucose (X), 4-O-methyl-1,2,3,6-tetra-O-acetyl-D-glucose, 6-O-methyl-1,2,3,4-tetra-O-acetyl-D-glucose (XI), 2,3-di-O-methyl-1,4,6-tri-O-acetyl-D-glucose, and 2,3,4,6-tetra-O-methyl-1-O-acetyl-D-glucose (XII). V gives a mixture containing XII, XI, X, and a di-O-methyl-tri-O-acetyl-

D-glucose. Atractylone Me ester gives XII.
 IT **18466-99-4P**
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of)
 RN 18466-99-4 HCAPLUS
 CN Atractyloside, diacetate, dipotassium salt (8CI) (CA INDEX NAME)



● 2 K

IT **18466-99-4P**
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of)

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L36 ANSWER 18 OF 46 USPATFULL on STN
 ACCESSION NUMBER: 2002:314708 USPATFULL
 TITLE: PRODUCTION OF ADENINE NUCLEOTIDE TRANSLOCATOR (ANT),
 NOVEL ANT LGANDS AND SCREENING ASSAYS THERRFOR
 INVENTOR(S): ANDERSON, CHRISTEN M., ENCINITAS, CA, UNITED STATES
 DAVIS, ROBERT E., SAN DIEGO, CA, UNITED STATES
 CLEVINGER, WILLIAM, VISTA, CA, UNITED STATES
 WILEY, SANDRA EILEEN, SAN DIEGO, CA, UNITED STATES
 MILLER, SCOTT W., SAN MARCOS, CA, UNITED STATES
 SZABO, TOMAS R., SAN DIEGO, CA, UNITED STATES
 GHOSH, SOUMITRA S., SAN DIEGO, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002177185	A1	20021128
APPLICATION INFO.:	US 1998-185904	A1	19981103 (9)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092		
NUMBER OF CLAIMS:	101		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	10 Drawing Page(s)		
LINE COUNT:	3588		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			
AB Compositions and methods are provided for producing adenine nucleotide			

translocator (ANT) polypeptides and fusion proteins, including the production and use of recombinant expression constructs having a regulated promoter. ANT ligands and compositions and methods for identifying ANT ligands, agents that bind ANT and agents that interact with ANT are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

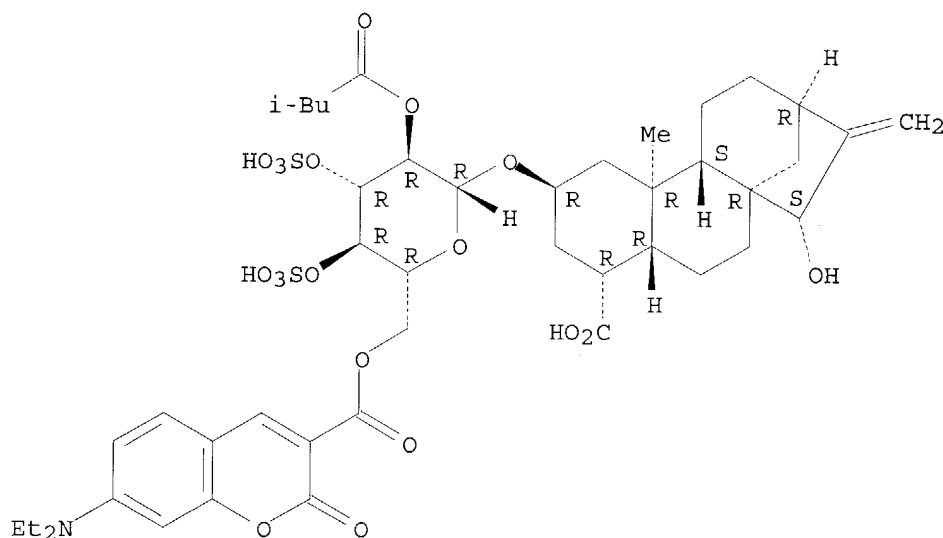
IT **267886-17-9P**

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

RN 267886-17-9 USPATFULL

CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-[[7-(diethylamino)-2-oxo-2H-1-benzopyran-3-yl]carbonyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo-β-D-glucopyranosyl]oxy]-15-hydroxy-, (2β,4α,15α)-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **267886-17-9P 267886-18-0P 267886-19-1P**

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

IT **267886-22-6P 267886-23-7P 267886-24-8P**

267886-25-9P 267886-26-0P 267886-27-1P

267886-28-2P 267886-29-3P 267886-30-6P

267886-31-7P 267886-50-0P 267886-51-1P

267886-56-6P 267886-57-7P

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

IT **84882-67-7P 267886-32-8P 267886-33-9P**

267886-34-0P 267886-35-1P 267886-36-2P

267886-37-3P 267886-38-4P 267886-39-5P

267886-40-8P 267886-41-9P 267886-42-0P

267886-43-1P 267886-44-2P 267886-45-3P

267886-46-4P 267886-47-5P 267886-48-6P

267886-49-7P

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

IT **267886-20-4P 267886-21-5DP, alkyldiamine derivs.**

267886-21-5P 267886-53-3P 267886-55-5P

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

L36 ANSWER 19 OF 46 USPATFULL on STN

ACCESSION NUMBER: 2002:308416 USPATFULL

TITLE: Compounds for altering mitochondrial function and cellular responses

INVENTOR(S): Pei, Yazhong, San Diego, CA, UNITED STATES
Moos, Walter H., Oakland, CA, UNITED STATES
Ghosh, Soumitra S., San Diego, CA, UNITED STATES

PATENT ASSIGNEE(S): MitoKor, San Diego, CA, 92121

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002173543	A1	20021121
	US 6552076	B2	20030422
APPLICATION INFO.:	US 2001-20090	A1	20011214 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-255803P	20001215 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092	
NUMBER OF CLAIMS:	18	
EXEMPLARY CLAIM:	1	
LINE COUNT:	2410	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds for treating diseases by altering mitochondrial function that affects cellular processes, as well as to compositions and methods related thereto. The compounds have the structure ##STR1##

wherein R.sub.1, R.sub.2, R.sub.3 and A are as defined herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

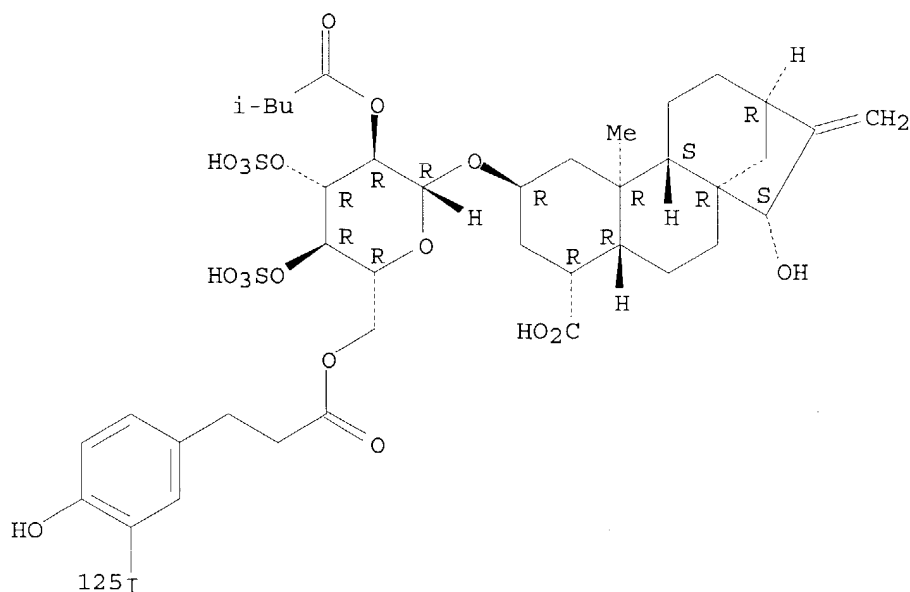
IT 437992-74-0

(radioligand; measurement of binding efficacy of amino acid derivs. in relation to mitochondrial function and cellular responses)

RN 437992-74-0 USPATFULL

CN 19-Norkaur-16-en-18-oic acid, 15-hydroxy-2-[[6-O-[3-[4-hydroxy-3-(iodo-125I)phenyl]-1-oxopropyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo-β-D-glucopyranosyl]oxy]-, (2β,4α,15α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 437992-74-0

(radioligand; measurement of binding efficacy of amino acid derivs. in relation to mitochondrial function and cellular responses)

L36 ANSWER 20 OF 46 USPATFULL on STN

ACCESSION NUMBER: 2002:22157 USPATFULL

TITLE: Production of adenine nucleotide translocator (ANT), novel ANT ligands and screen for reformation

INVENTOR(S): Anderson, Christen
Davis, Robert E.,
Clevenger, William,
Wiley, Sandra Eileen,
Miller, Scott W., S
Szabo, Tomas R., Sa
Ghosh, Soumitra S.,
Moos, Walter H., Oak
Pei, Yazhong, San Di

UNITED STATES
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APP

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002012992	A1	20020131
APPLICATION INFO.:	US 2001-810644	A1	20010314 (9)
RELATED APPLN. INFO.:	Division of Ser. No. US 1999-393441, filed on 8 Sep 1999, PENDING Continuation-in-part of Ser. No. US 1998-185904, filed on 3 Nov 1998, PENDING		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092		
NUMBER OF CLAIMS:	112		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	14 Drawing Page(s)		
LINE COUNT:	4467		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods are provided for producing adenine nucleotide translocator (ANT) polypeptides and fusion proteins, including the

production and use of recombinant expression constructs having a regulated promoter. ANT ligands and compositions and methods for identifying ANT ligands, agents that bind ANT and agents that interact with ANT are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

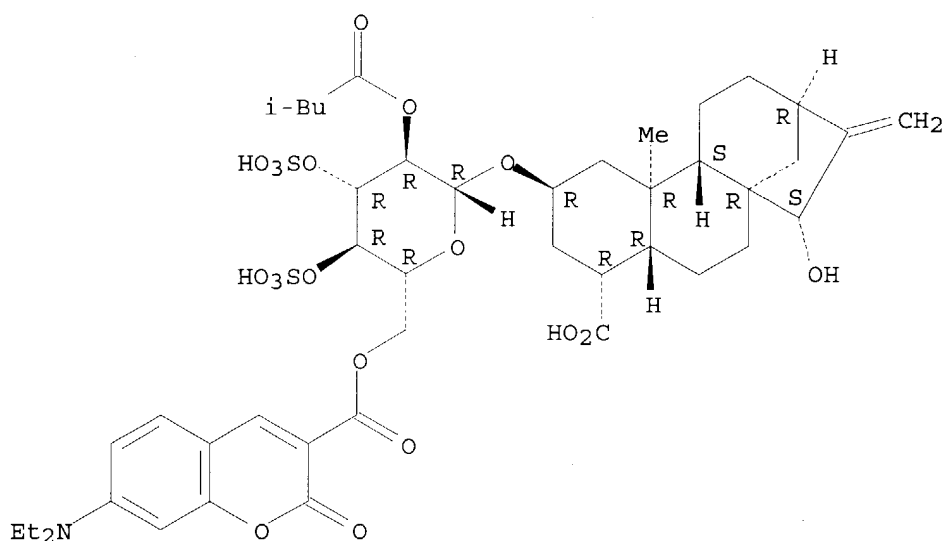
IT 267886-17-9P

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

RN 267886-17-9 USPATFULL

CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-[[7-(diethylamino)-2-oxo-2H-1-benzopyran-3-yl]carbonyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo- β -D-glucopyranosyl]oxy]-15-hydroxy-, (2 β ,4 α ,15 α)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 267886-17-9P 267886-18-0P 267886-19-1P

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

IT 267886-22-6P 267886-23-7P 267886-24-8P

267886-25-9P 267886-26-0P 267886-27-1P

267886-28-2P 267886-29-3P 267886-30-6P

267886-31-7P 267886-50-0P 267886-51-1P

267886-56-6P 267886-57-7P

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

IT 84882-67-7P 267886-32-8P 267886-33-9P

267886-34-0P 267886-35-1P 267886-36-2P

267886-37-3P 267886-38-4P 267886-39-5P

267886-40-8P 267886-41-9P 267886-42-0P

267886-43-1P 267886-44-2P 267886-45-3P

267886-46-4P 267886-47-5P 267886-48-6P

267886-49-7P

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

IT 267886-20-4P 267886-21-5DP, alkylidiamine derivs.

267886-21-5P 267886-53-3P 267886-55-5P

(cloning and production of human adenine nucleotide translocator and the

synthesis and screening assays for novel ligands)

L36 ANSWER 21 OF 46 USPATFULL on STN

ACCESSION NUMBER: 2001:212150 USPATFULL

TITLE: Production of adenine nucleotide translocator (ANT),

novel ANT ligands and screening assays therefor

INVENTOR(S): Anderson, Christen M., Encinitas, CA, United States

Davis, Robert E., San Diego, CA, United States

Clevenger, William, Oceanside, CA, United States

Wiley, Sandra Eileen, San Diego, CA, United States

Miller, Scott W., San Marcos, CA, United States

Szabo, Tomas R., San Diego, CA, United States

Ghosh, Soumitra S., San Diego, CA, United States

Moss, Walter H., Oakland, CA, United States

Pei, Yazhong, San Diego, CA, United States

NUMBER	KIND	DATE
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PATENT INFORMATION:	US 2001044144	A1	20011122
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APPLICATION INFO.:	US 2001-811094	A1	20010314 (9)
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RELATED APPLN. INFO.:	Division of Ser. No. US 1999-393441, filed on 8 Sep 1999, PENDING Continuation-in-part of Ser. No. US 1998-185904, filed on 3 Nov 1998, PENDING		
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DOCUMENT TYPE:	Utility		
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FILE SEGMENT:	APPLICATION		
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LEGAL REPRESENTATIVE:	SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092		
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NUMBER OF CLAIMS:	112		
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EXEMPLARY CLAIM:	1		
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NUMBER OF DRAWINGS:	14 Drawing Page(s)		
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LINE COUNT:	4432		
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods are provided for producing adenine nucleotide translocator (ANT) polypeptides and fusion proteins, including the production and use of recombinant expression constructs having a regulated promoter. ANT ligands and compositions and methods for identifying ANT ligands, agents that bind ANT and agents that interact with ANT are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

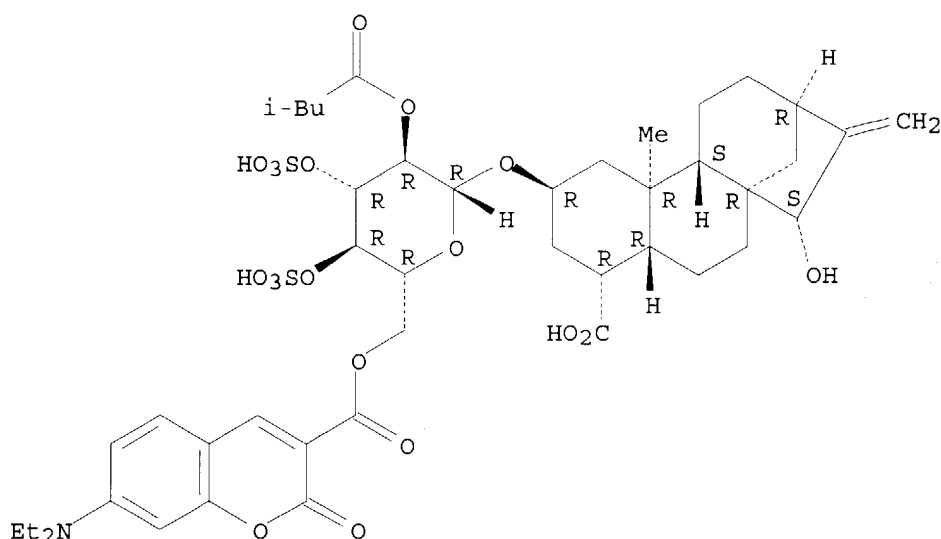
IT 267886-17-9P

(cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

RN 267886-17-9 USPATFULL

CN 19-Norkaur-16-en-18-oic acid, 2-[[6-O-[[7-(diethylamino)-2-oxo-2H-1-benzopyran-3-yl]carbonyl]-2-O-(3-methyl-1-oxobutyl)-3,4-di-O-sulfo-β-D-glucopyranosyl]oxy]-15-hydroxy-, (2β,4α,15α)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



- IT 267886-17-9P 267886-18-0P 267886-19-1P
 (cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)
- IT 267886-22-6P 267886-23-7P 267886-24-8P
 267886-25-9P 267886-26-0P 267886-27-1P
 267886-28-2P 267886-29-3P 267886-30-6P
 267886-31-7P 267886-50-0P 267886-51-1P
 267886-56-6P 267886-57-7P
 (cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)
- IT 84882-67-7P 267886-32-8P 267886-33-9P
 267886-34-0P 267886-35-1P 267886-36-2P
 267886-37-3P 267886-38-4P 267886-39-5P
 267886-40-8P 267886-41-9P 267886-42-0P
 267886-43-1P 267886-44-2P 267886-45-3P
 267886-46-4P 267886-47-5P 267886-48-6P
 267886-49-7P
 (cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)
- IT 267886-20-4P 267886-21-5DP, alkylidiamine derivs.
 267886-21-5P 267886-53-3P 267886-55-5P
 (cloning and production of human adenine nucleotide translocator and the synthesis and screening assays for novel ligands)

=> d ibib abs 22-41

L36 ANSWER 22 OF 46 MEDLINE on STN
 ACCESSION NUMBER: 86130475 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 3004431
 TITLE: 6'-O-dansyl-gamma-aminobutyryl atractyloside, a fluorescent probe of the ADP/ATP carrier: exploration of conformational changes of the membrane-bound ADP/ATP carrier elicited by substrates and inhibitors.
 AUTHOR: Boulay F; Brandolin G; Vignais P V
 SOURCE: Biochemical and biophysical research communications, (1986 Jan 14) 134 (1) 266-71.
 Journal code: 0372516. ISSN: 0006-291X.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198603
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860314

AB A fluorescent atractyloside analogue, the 6'-O-dansyl-gamma-aminobutyryl atractyloside (DGA), has been used to probe the binding of the inhibitors carboxyatractyloside (CATR) and bongkrekic acid (BA) and nucleotide substrates to the membrane-bound ADP/ATP carrier protein in beef heart mitochondria. Binding and release of DGA were followed by fluorescence responses. Specifically bound DGA was fully released by CATR alone, or by BA in the presence of micromolar amounts of ADP. In the absence of the inhibitors, ADP increased the rate of the specific binding of DGA. The effect of ADP was shared by transportable nucleotides. Non transportable nucleotides were ineffective. These data are consistent with the previously described CATR and BA conformations of the ADP/ATP carrier that are able to bind CATR and BA respectively, the transition between the two conformations being accelerated by micromolar concentrations of transportable nucleotides.

L36 ANSWER 23 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1999:140887 BIOSIS
DOCUMENT NUMBER: PREV199900140887
TITLE: Characterization of a dCTP transport activity reconstituted from human mitochondria.
AUTHOR(S): Bridges, Edward G.; Jiang, Zaoli; Cheng, Yung-Chi [Reprint author]
CORPORATE SOURCE: Dep. Pharmacology, Yale Univ. Sch. Med., P.O. Box 802066, New Haven, CT 06520, USA
SOURCE: Journal of Biological Chemistry, (Feb. 19, 1999) Vol. 274, No. 8, pp. 4620-4625. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Mar 1999
Last Updated on STN: 31 Mar 1999

AB A protein fraction of mitochondria from human acute lymphocytic leukemia cells, which could be reconstituted into proteoliposomes to have dCTP transport activity, has been partially purified by hydroxyapatite and blue Sepharose chromatography. The dCTP transport activity in proteoliposomes was time-dependent and could be activated by Ca^{2+} and to a lesser extent by Mg^{2+} . None of the other divalent cations tested could activate the transport activity. The K_m value of dCTP in the presence of Ca^{2+} was shown to be 3 μM . dCDP but not dCMP or dCyd could inhibit the transport activity. Other deoxynucleoside triphosphates could also inhibit the uptake of dCTP with the potency $\text{dGTP} = \text{dATP} > \text{TTP}$. Although ATP could competitively inhibit dCTP uptake with a K_i value of 8 μM , the reconstituted dCTP uptake activity was not sensitive to the **ATP/ADP carrier** inhibitor **atractyloside** or the sulfhydryl reagent N-ethylmaleimide. This suggests that the dCTP transport system studied is not the same as the **ATP/ADP carrier**. In conclusion, these studies describe the first functionally reconstituted mitochondrial carrier that displays an efficient transport activity for dCTP.

L36 ANSWER 24 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on

STN

ACCESSION NUMBER: 1998:475916 BIOSIS
 DOCUMENT NUMBER: PREV199800475916
 TITLE: Bax and adenine nucleotide translocator cooperate in the mitochondrial control of apoptosis.
 AUTHOR(S): Marzo, Isabel; Brenner, Catherine; Zamzami, Naoufal; Juergensmeier, Juliane M.; Susin, Santos A.; Vieira, Helena L. A.; Prevost, Marie-Christine; Xie, Zhihua; Matsuyama, Shigemi; Reed, John C.; Kroemer, Guido [Reprint author]
 CORPORATE SOURCE: CNRS, UPR 420, 19 rue Guy Moquet, F-94801 Villejuif, France
 SOURCE: Science (Washington D C), (Sept. 25, 1998) Vol. 281, No. 5385, pp. 2027-2031. print.
 CODEN: SCIEAS. ISSN: 0036-8075.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 5 Nov 1998
 Last Updated on STN: 5 Nov 1998

AB The proapoptotic Bax protein induces cell death by acting on mitochondria. Bax binds to the permeability transition pore complex (PTPC), a composite proteaceous channel that is involved in the regulation of mitochondrial membrane permeability. Immunodepletion of Bax from PTPC or purification of PTPC from Bax-deficient mice yielded a PTPC that could not permeabilize membranes in response to **atractyloside**, a proapoptotic ligand of the adenine nucleotide translocator (**ANT**). Bax and **ANT** coimmunoprecipitated and interacted in the yeast two-hybrid system. Ectopic expression of Bax induced cell death in wild-type but not in **ANT**-deficient yeast. Recombinant Bax and purified **ANT**, but neither of them alone, efficiently formed **atractyloside**-responsive channels in artificial membranes. Hence, the proapoptotic molecule Bax and the constitutive mitochondrial protein **ANT** cooperate within the PTPC to increase mitochondrial membrane permeability and to trigger cell death.

L36 ANSWER 25 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1998:116326 BIOSIS
 DOCUMENT NUMBER: PREV199800116326
 TITLE: Complexes between porin, hexokinase, mitochondrial creatine kinase and adenylate translocator display properties of the permeability transition pore. Implication for regulation of permeability transition by the kinases.
 AUTHOR(S): Beutner, Gisela; Rueck, Alexander; Riede, Birgit; Brdiczka, Dieter [Reprint author]
 CORPORATE SOURCE: Fac. Biol., Univ. Konstanz, D-78434 Konstanz, Germany
 SOURCE: Biochimica et Biophysica Acta, (Jan. 5, 1998) Vol. 1368, No. 1, pp. 7-18. print.
 CODEN: BBACAQ. ISSN: 0006-3002.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 5 Mar 1998
 Last Updated on STN: 5 Mar 1998

AB Complexes between hexokinase, outer membrane porin, and the adenylate translocator (**ANT**) were recently found to establish properties of the mitochondrial permeability transition pore in a reconstituted system. The complex was extracted by 0.5% Triton X-100 from rat brain membranes and separated by anion exchanger chromatography. The molecular weight was approximately 400 kDa suggesting tetramers of hexokinase (monomer 100 kDa). By the same method a porin, creatine kinase octamer, **ANT** complex was isolated and reconstituted in liposomes. Vesicles containing the reconstituted complexes both retained ATP that could be

used by either kinase to phosphorylate external creatine or glucose. **Atractyloside** inhibited this activity indicating that the **ANT** was involved in this process and was functionally reconstituted (1). Exclusively from the hexokinase complex containing liposome internal malate or ATP was released by addition of Ca^{2+} in a N-methylVal-4-cyclosporin sensitive way, suggesting that the hexokinase porin **ANT** complex might include the permeability transition pore (PTP). The Ca^{2+} dependent opening of the PTP-like structure was inhibited by ADP (apparent I_{50} , 8 μM) and ATP (apparent I_{50} , 84 μM). Also glucose inhibited the PTP-like activity, while glucose-6-phosphate abolished this effect. Although porin and **ANT** were functionally active in vesicles containing the creatine kinase octamer complex, Ca^{2+} did not induce a release of internal substrates. However, after dissociation of the creatine kinase octamer, the complex exhibited PTP-like properties and the vesicles liberated internal metabolites upon addition of Ca^{2+} . The latter process was also inhibited by N-methylVal-4-cyclosporin. The activity of peptidyl-prolyl-cis-trans-isomerase (representing cyclophilin) was followed during complex isolation. Cyp D was co-purified with the hexokinase complex, while it was absent in the creatine kinase complex. The inhibitory effect of N-methylVal-4-cyclosporin on the creatine kinase complex may be explained by direct interaction with the creatine kinase dimer that appeared to support octamer formation.

L36 ANSWER 26 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1997:41386 BIOSIS

DOCUMENT NUMBER: PREV199799333374

TITLE: Peroxidative modification of a membrane protein.
Conformation-dependent chemical modification of adenine nucleotide translocase in Cu^{2+} /tert-butyl hydroperoxide treated mitochondria.

AUTHOR(S): Giron-Calle, Julio; Schmid, Harald H. O. [Reprint author]

CORPORATE SOURCE: Hormel Inst., Univ. Minn., Austin, MN 55912, USA

SOURCE: Biochemistry, (1996) Vol. 35, No. 48, pp. 15440-15446.
CODEN: BICHAW. ISSN: 0006-2960.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 28 Jan 1997

Last Updated on STN: 28 Jan 1997

AB Peroxidative treatment of rat heart mitochondria results in a gradual increase of the apparent molecular weight of the adenine nucleotide translocase (**ANT**) by up to 1.2 kDa. **ANT** isolated from mitochondria treated with 1 mM tert-butyl hydroperoxide and 5-40 μM Cu^{2+} for 1 h at 37 degree C exhibited a progressive loss of lysine, cysteine, arginine, and valine residues compared to native **ANT**. N-Ethylmaleimide, dithiothreitol, and the specific inhibitor of **ANT**, **carboxyatractyloside** (CAT), inhibited the peroxidation-induced molecular weight shift without inhibiting lipid peroxidation, which is believed to be the primary cause of the observed **ANT** modification. Bongkreikic acid, which stabilizes **ANT** in a conformation different from that brought about by CAT, did not inhibit the **ANT** molecular weight shift. Dithiothreitol, as well as CAT, was found to protect **ANT** against most of the losses of amino acid residues, indicating that alteration of sulfhydryl residues is required for chemical modification of, not only cysteine, but also lysine, arginine, and valine. We conclude that the peroxidative modification of **ANT** is conformation-dependent and involves chemical modification of cysteine as a critical step.

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STN

ACCESSION NUMBER: 1996:152096 BIOSIS
 DOCUMENT NUMBER: PREV199698724231
 TITLE: Activity of the mitochondrial multiple conductance channel is independent of the adenine nucleotide translocator.
 AUTHOR(S): Lohret, Timothy A.; Murphy, Robert C.; Drgon, Tomas; Kinnally, Kathleen W. [Reprint author]
 CORPORATE SOURCE: Wadsworth Cent., New York State Dep. Health, Empire State Plaza, PO Box 509, Albany, NY 12201-0509, USA
 SOURCE: Journal of Biological Chemistry, (1996) Vol. 271, No. 9, pp. 4846-4849.
 CODEN: JBCHA3. ISSN: 0021-9258.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 11 Apr 1996
 Last Updated on STN: 11 Apr 1996

AB The functional relationship between the adenine nucleotide translocator (**ANT**) and the mitochondrial multiple conductance channel (MCC) was investigated using patch-clamp techniques. MCC activity with the same conductance, ion selectivity, voltage dependence, and peptide sensitivity could be reconstituted from inner membrane fractions derived from mitochondria of **ANT**-deficient and wild-type *Saccharomyces cerevisiae*. In addition, the MCC activity of mouse kidney mitoplasts was unaffected by **carboxyatractylamide**, a known inhibitor of **ANT** and inducer of a permeability transition. These results suggest that MCC activity is independent of **ANT**.

L36 ANSWER 28 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1996:282888 BIOSIS
 DOCUMENT NUMBER: PREV199699005244
 TITLE: Mitochondrial control of nuclear apoptosis.
 AUTHOR(S): Zamzami, Naoufal; Susin, Santos A.; Marchetti, Philippe; Hirsch, Tamara; Gomez-Monterrey, Isabel; Castedo, Maria; Kroemer, Guido [Reprint author]
 CORPORATE SOURCE: CNRS-UPR420, 19 rue Guy Moquet, B.P.8, F-94801 Villejuif, France
 SOURCE: Journal of Experimental Medicine, (1996) Vol. 183, No. 4, pp. 1533-1544.
 CODEN: JEMEAU. ISSN: 0022-1007.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 25 Jun 1996
 Last Updated on STN: 25 Jun 1996

AB Anucleate cells can be induced to undergo programmed cell death (PCD), indicating the existence of a cytoplasmic PCD pathway that functions independently from the nucleus. Cytoplasmic structures including mitochondria have been shown to participate in the control of apoptotic nuclear disintegration. Before cells exhibit common signs of nuclear apoptosis (chromatin condensation and endonuclease-mediated DNA fragmentation), they undergo a reduction of the mitochondrial transmembrane potential ($\Delta\psi$) that may be due to the opening of mitochondrial permeability transition (PT) pores. Here, we present direct evidence indicating that mitochondrial PT constitutes a critical early event of the apoptotic process. In a cell-free system combining purified mitochondria and nuclei, mitochondria undergoing PT suffice to induce chromatin condensation and DNA fragmentation. Induction of PT by pharmacological agents augments the apoptosis-inducing potential of mitochondria. In contrast, prevention of PT by pharmacological agents impedes nuclear apoptosis, both in vitro and in vivo. Mitochondria from

hepatocytes or lymphoid cells undergoing apoptosis, but not those from normal cells, induce the disintegration of isolated Hela nuclei. A specific ligand of the mitochondrial adenine nucleotide translocator (**ANT**), bongkrekic acid, inhibits PT and reduces apoptosis induction by mitochondria in a cell-free system. Moreover, it inhibits the induction of apoptosis in intact cells. Several pieces of evidence suggest that the proto-oncogene product Bcl-2 inhibits apoptosis by preventing mitochondrial PT. First, to inhibit nuclear apoptosis, Bcl-2 must be localized in mitochondrial but not in nuclear membranes. Second, transfection-enforced hyperexpression of Bcl-2 directly abolishes the induction of mitochondrial PT in response to a protonophore, a pro-oxidant, as well as to the **ANT** ligand **atractyloside**, correlating with its apoptosis-inhibitory effect. In conclusion, mitochondrial PT appears to be a critical step of the apoptotic cascade.

L36 ANSWER 29 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1996:65241 BIOSIS
 DOCUMENT NUMBER: PREV199698637376
 TITLE: Developmental changes of the adenine nucleotide translocation in rat brain.
 AUTHOR(S): Schoenfeld, Peter [Reprint author]; Bohnensack, Ralf
 CORPORATE SOURCE: Inst. Biochemie, Medizinische Fakultät der Otto-von-Guericke-Universität Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany
 SOURCE: Biochimica et Biophysica Acta, (1995) Vol. 1232, No. 1-2, pp. 75-80.
 CODEN: BBACAQ. ISSN: 0006-3002.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 9 Feb 1996
 Last Updated on STN: 10 Feb 1996

AB The perinatal development of the adenine nucleotide translocation in isolated rat brain mitochondria was studied. For that purpose the content of the adenine nucleotide translocase (**ANT**), the activity of adenine nucleotide translocation and the control of the **ANT** protein over State 3 respiration were estimated. From the newborn to the adult state there was a 4-fold increase in State 3 respiration which was paralleled by a 3-fold increase in the respiratory control ratio. The capacity of uncoupled respiration exceeded that of State 3 respiration in all developmental stages indicating that the activity of oxidative phosphorylation is influenced by that of **ANT** and/or ATP synthase. The content of the **ANT** protein, measured as bound pmoles of (3H)**atractyloside** per mg mitochondrial protein, increased more than 2-fold from birth to adulthood in the first three postnatal weeks. The size of the exchangeable matrix (ATP + ADP)-pool was only slightly expanded during the same period. The translocation activity increased 2-fold from the newborn to the adult state and was a linear function of the **ANT** protein. Control of the **ANT** protein over State 3 respiration (quantified as flux control coefficient, C-**ANT**-Jo), was remarkable in brain mitochondria from newborn rats (C-**ANT**-Jo = 0.45 ± 0.15), but declined during further development (C-**ANT**-Jo = 0.11 ± 0.03, at the 20th day). The obtained results suggest that the postnatal enrichment of the **ANT** protein in rat brain mitochondria is an essential factor for the development of oxidative phosphorylation capacity in the early postnatal period.

L36 ANSWER 30 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1994:82575 BIOSIS
 DOCUMENT NUMBER: PREV199497095575
 TITLE: The regulation of pyruvate dehydrogenase activity in pea leaf mitochondria: The effect of respiration and oxidative phosphorylation.
 AUTHOR(S): Moore, Anthony L. [Reprint author]; Gemel, Joanna; Randall, Douglas D.
 CORPORATE SOURCE: Biochem. Dep., Univ. Sussex, Falmer, Brighton BN1 9QG, UK
 SOURCE: Plant Physiology (Rockville), (1993) Vol. 103, No. 4, pp. 1431-1435.
 CODEN: PLPHAY. ISSN: 0032-0889.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 22 Feb 1994
 Last Updated on STN: 23 Feb 1994

AB The regulation of the pea (*Pisum sativum*) leaf mitochondrial pyruvate dehydrogenase complex by respiratory rate and oxidative phosphorylation has been investigated by measuring the respiratory activity, the redox poise of the quinone pool (Q-pool), and mitochondrial pyruvate dehydrogenase (mtPDC) activity under various metabolic conditions. It was found that, under state 4 conditions, mtPDC activity was unaffected by either the addition of succinate, 2-oxoglutarate, or glycine or the overall respiratory rate and redox poise of the Q-pool but was partially inhibited by NADH due to product inhibition. In the presence of ADP significant inactivation of PDC, which was sensitive to oligomycin, was observed with all substrates, apart from pyruvate, suggesting that inactivation was due to ATP formation. Inactivation of PDC by ADP addition was observed even in the presence of **carboxyattractyloside**, an inhibitor of the **ATP/ADP translocator**, suggesting that other mechanisms to facilitate the entry of adenylates, in addition to the adenylate carrier, must exist in plant mitochondria.

L36 ANSWER 31 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1993:583336 BIOSIS
 DOCUMENT NUMBER: PREV199497002706
 TITLE: Increase in the adenine nucleotide translocase protein contributes to the perinatal maturation of respiration in rat liver mitochondria.
 AUTHOR(S): Schoenfeld, Peter [Reprint author]; Fritz, Simone; Halangk, Walter; Bohnensack, Ralf
 CORPORATE SOURCE: Inst. Biochem., Med. Akad. Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany
 SOURCE: Biochimica et Biophysica Acta, (1993) Vol. 1144, No. 3, pp. 353-358.
 CODEN: BBACAQ. ISSN: 0006-3002.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 28 Dec 1993
 Last Updated on STN: 5 Mar 1994

AB An assay based on the high-affinity binding of tritium-labelled **attractyloside** to the adenine nucleotide translocase (**ANT**) was developed for estimation of its content in samples of mitochondria, cells and tissue homogenate. The assay was used to study the developmental change of the **ANT** protein concentration in perinatal rat liver. Within the last 3 days before birth the content of the **ANT** protein per mg tissue protein increased from 29 to 45% of the maximum value found 2 days after birth. A similar developmental change of the **ANT** protein was found in isolated mitochondria, demonstrating that the perinatal increase in the **ANT** protein

content was due mainly to a mitochondrial differentiation process and not the result of an increase in the number of mitochondria per cell. A close proportionality between the **ANT** protein and the ADP-stimulated respiration of liver homogenate was found in the perinatal period from 3 days before to 2 days after birth. This finding suggests that the developmental change in the **ANT** protein content plays an important role in the onset of oxidative phosphorylation after birth.

L36 ANSWER 32 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1993:48975 BIOSIS
DOCUMENT NUMBER: PREV199395025277
TITLE: Adenine nucleotide translocase greatly increases the partition of trinitrophenyl-ATP into reduced Triton X-100 micelles.
AUTHOR(S): Tummino, Peter J.; Gafni, Ari
CORPORATE SOURCE: Inst. Gerontol., Dep. Biol. Chem., Univ. Mich., Ann Arbor, Mich. 48109, USA
SOURCE: Biophysical Journal, (1992) Vol. 63, No. 4, pp. 1071-1080. CODEN: BIOJAU. ISSN: 0006-3495.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Jan 1993
Last Updated on STN: 14 Jan 1993

AB The presence of adenine nucleotide translocase (**ANT**) was found to greatly enhance the partitioning of the ATP analog 2',3'-O-(2,4,6-trinitrophenyl)-adenosine 5'-triphosphate (TNP-ATP) into reduced Triton X-100 micelles. The protein's effect was studied through the quenching of fluorescence of purified **ANT**, irreversibly inhibited by **carboxyatractyloside** (CAT), solubilized in reduced Triton X-100 micelles. The dependence of quenching of the protein's time-resolved tryptophan fluorescence of TNP-ATP concentration was measured and found to follow a Stern-Volmer mechanism. However, the calculated quenching constant was too large to be accounted for by the aqueous TNP-ATP concentration. Experiments were therefore conducted to determine the partitioning of the quencher between the three phases present: aqueous, protein-free micelle, and protein micelle; a system also described by the equation of Omann, G.M., and M. Glaser (1985. Biophys. J. 47:623-627.). By measuring the dependence of the apparent quenching rate constant of the protein concentration and protein/micelle ratios, this equation was used to calculate both the quencher partition coefficient into protein-free micelles (P-m) and into protein-micelles (P-pm), as well as the bimolecular quenching rate constant (K-pm) in protein micelles. From the quenching experiments, K-pm = 5.0 times 10⁻⁸ M⁻¹ s⁻¹, P-m = 290 and P-pm = 7.0 times 10⁻³. P-m was also determined independently by pyrene quenching experiment to be 325, and by a rapid filtration experiment to be 450. Clearly, the presence of the integral membrane protein **ANT**-CAT in reduced Triton X-100 micelles greatly increases the partition of TNP-ATP into the micelle. **ANT** alters the properties and thus, the structure of the detergent micelle, which has direct implications for the use of detergent micelles as a model system for membrane proteins and may indicate that analogous effects occur in the mitochondrial membrane.

L36 ANSWER 33 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1986:243518 BIOSIS
DOCUMENT NUMBER: PREV198682008022; BA82:8022
TITLE: IMPORT OF GLYOXYSOMAL MALATE DEHYDROGENASE PRECURSOR INTO GLYOXYSOMES A HETEROLOGOUS IN-VITRO SYSTEM.
AUTHOR(S): GIETL C [Reprint author]; HOCK B

CORPORATE SOURCE: DEP BOTANY, FAC AGRICULTURE AND HORTICULTURE, TECHNICAL
UNIV MUNICH, D-8050 FREISING 12, FRG
SOURCE: Planta (Heidelberg), (1986) Vol. 167, No. 1, pp. 87-93.
CODEN: PLANAB. ISSN: 0032-0935.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 7 Jun 1986
Last Updated on STN: 7 Jun 1986

AB A heterologous in-vitro system is described for the import of the precursor to glyoxysomal malate dehydrogenase from watermelon (*Citrullus vulgaris* Schrad., cv. Kleckey's Sweet Number 6) cotyledons into glyoxysomes from castor-bean (*Ricinus communis* L.) endosperm. The 41-kDa precursor is posttranslationally sequestered and correctly processed to the mature 33-kDa subunit by a crude glyoxysomal fraction or by glyoxysomes purified on a sucrose gradient. The import and the cleavage of the extrasequence is not inhibited by metal chelators such as 1,10-phenanthroline and ethylenediaminetetraacetic acid. Uncouplers (carbonylcyanide m-chlorophenylhydrazone), ionophores (valinomycin), or inhibitors of oxidative phosphorylation (oligomycin) and **ATP-ADP translocation (carboxyatractyloside)** do not interfere, thus indicating the independence of the process of import by the organelle from the energization of the glyoxysomal membrane.

L36 ANSWER 34 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1985:231067 BIOSIS
DOCUMENT NUMBER: PREV198579011063; BA79:11063
TITLE: PROLIFERATION MACROMOLECULAR SYNTHESIS AND ENERGY
METABOLISM OF IN-VITRO GROWN EHRlich ASCITES TUMOR CELLS
AFTER INHIBITION OF **ATP-ADP TRANSLOCATION BY ATRACTYLOSIDE.**
AUTHOR(S): PICK-KOBER K-H [Reprint author]; SCHNEIDER F
CORPORATE SOURCE: PHYSIOL-CHEM INST UNIV MARBURG, BUNDESREPUBLIK DEUTSCHLAND
SOURCE: European Journal of Cell Biology, (1984) Vol. 34, No. 2,
pp. 323-329.
CODEN: EJCBDN. ISSN: 0171-9335.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

AB In the presence of 3 mM atractyloside, growth of in vitro cultured Ehrlich ascites tumor cells is inhibited by 70% within 24 h. Viability of the cells is not severely affected (dye exclusion test). Incorporation of 2-[14C]-thymidine and U-[14C]-Leu into acid insoluble precipitate were reduced by 80% or 20%, respectively, as compared to controls. Flow cytometric analysis of cell cycle progression revealed a retardation rather than an arrest of cell growth by atractyloside. Morphological changes of the cells primarily concern mitochondria which are spherical shaped with translucent matrix rid of cristae. After transfer of atractyloside treated cells to normal medium, proliferation and macromolecular synthesis normalized within 3-6 h. At 3 mM of atractyloside, glucose consumption of the cells increased by 25%, lactate production by 30%. Lactate/glucose ratio was 1.9 after 24 h. O₂ uptake was reduced by 35% after 12 h. The [ATP]/[ADP] ratio of the whole cells runs through a maximum between 12 and 18 h. The ratio never falls below 5.0. The ATP/ADP concentration ratio in the mitochondrial and extramitochondrial compartment were increased as compared to controls. ΔG of ATP hydrolysis of the intact cells was in a normal range (-50 kJ), energy charge was 0.86 (controls 0.88). Transport of amino acids, uptake of glucose and activity of Na⁺, K⁺-ATPase of the plasma membrane

were not impaired by 3 mM atractyloside. DNA synthesis and cell proliferation inhibiting activity of atractyloside does not correlate in a simple manner with the energy state of the cells in the presence of the drug.

L36 ANSWER 35 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1980:235414 BIOSIS
DOCUMENT NUMBER: PREV198070027910; BA70:27910
TITLE: A PHOSPHORUS-31 NMR STUDY OF THE CROSS MEMBRANE PH GRADIENT INDUCED BY ATP HYDROLYSIS IN MITOCHONDRIA.
AUTHOR(S): OGAWA S [Reprint author]; SHEN C; CASTILLO C L
CORPORATE SOURCE: BELL LAB, MURRAY HILL, NJ 07974, USA
SOURCE: Biochimica et Biophysica Acta, (1980) Vol. 590, No. 2, pp. 159-169.
CODEN: BBACAQ. ISSN: 0006-3002.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

AB ³¹P-NMR was used to study the increase of ΔpH in mitochondria by externally added ATP. Freshly prepared rat liver mitochondria were treated with N-ethylmaleimide to inhibit the exchange between internal and external P_i. Upon addition of ATP, phosphocreatine (30 mM) and creatine kinase to a NMR sample of mitochondria suspension (.apprx. 120 mg protein/ml) at 0° C, an increase of ΔpH by .apprx. 0.5 pH unit was observed. The increased ΔpH could not be maintained, but slowly decayed along with the increase of external ADP/ATP ratio. Further addition of valinomycin to the suspension induced a larger ΔpH (.apprx. 1) which was maintained by the increased rate of internal ATP hydrolysis as seen in the growth of the internal P_i peak intensity in NMR spectra and the concomitant decrease of the external phosphocreatine peak. The external P_i and ATP peaks stayed virtually constant. When **carboxyatractyloside** was added to inhibit the **ATP/ADP translocase**, the internal P_i increase was stopped and the ΔpH decayed. These observations in conjunction with those made earlier in respiring mitochondria clearly show the reversible nature of the ATPase function in which the internal ATP hydrolysis is associated with outward pumping of protons.

L36 ANSWER 36 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1979:197931 BIOSIS
DOCUMENT NUMBER: PREV197968000435; BA68:435
TITLE: MITOCHONDRIAL ADENINE NUCLEOTIDE TRANSLOCASE.
AUTHOR(S): PANOV A V [Reprint author]; LYAKHOVICH V V
CORPORATE SOURCE: INST CLIN EXP MED, SIB BRANCH, ACAD MED SCI USSR, NOVOSIBIRSK, USSR
SOURCE: Bioorganicheskaya Khimiya, (1978) Vol. 4, No. 1, pp. 5-18.
CODEN: BIKHD7. ISSN: 0132-3423.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: RUSSIAN

AB This review discussed the properties and mechanism of highly specific ADP and ATP transport through the inner mitochondrial membrane, catalyzed by the hydrophobic protein adenine nucleotide translocase (**ANT**). Such properties of the overall mechanism of oxidative phosphorylation as nucleotide specificity, kinetics, temperature and pH dependence of ATP synthesis or hydrolysis are determined by **ANT**. The transport exhibits an obligatory coupled counter-exchange of endogenous and exogenous adenine nucleotides and depends on the metabolic state of

mitochondria. The energization of mitochondria favors the exchange of exogenous ADP against endogenous ATP. Specific inhibitors of **ANT**, e.g. **atractyloside** (AT), **4-carboxyatractyloside** (CAT), bongkrekic acid (BA) and long chain acyl-CoA's are useful in studies of adenine nucleotide transport. These inhibitors to various extent compete with ADP and ATP for binding sites on the carrier. AT, CAT and acyl-CoA inhibit the AN transport from the outer side and BA from the inner side of the inner mitochondrial membrane. The current hypotheses on the mechanism of adenine nucleotide carrier functioning are discussed.

L36 ANSWER 37 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1974:178997 BIOSIS
DOCUMENT NUMBER: PREV197458008691; BA58:8691
TITLE: STUDIES ON MITOCHONDRIAL CREATINE PHOSPHO KINASE PART 1 RAT SKELETAL MUSCLE MITOCHONDRIA.
AUTHOR(S): MOORE C L; STRASBERG P M; KOVAC C
SOURCE: Texas Reports on Biology and Medicine, (1973) Vol. 31, No. 3, pp. 367-384.
CODEN: TRBMAV. ISSN: 0040-4675.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: Unavailable

L36 ANSWER 38 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1998135493 EMBASE
TITLE: Fatty acid-mediated uncoupling of potato tuber mitochondria.
AUTHOR: Saviani E.E.; Martins I.S.
CORPORATE SOURCE: I.S. Martins, Departamento de Bioquimica, Institute de Biologia, Universidade Estadual de Campinas, CP 6109, Campinas SP, CEP 13083-970, Brazil
SOURCE: Biochemistry and Molecular Biology International, (1998) 44/4 (833-839).
Refs: 18
ISSN: 1039-9712 CODEN: BMBIES
COUNTRY: Australia
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The present work examined whether the **ATP/ADP carrier**, other than the plant uncoupling mitochondrial protein, participates in free fatty acid-mediated uncoupling of potato tuber mitochondria. The basal respiration rate of succinate-energized mitochondria was stimulated by a low concentration of palmitate (20µM). This uncoupling was reversed by 10µM **carboxyatractyloside** and by the subsequent addition of 0.1% bovine serum albumin. The decrease in membrane potential caused by palmitate was suppressed by **carboxyatractyloside** (1µM) and, to a lesser degree, by bongkrekate (20µM). GTP could also reversed this decrease via a **carboxyatractyloside**-independent mechanism. These results indicate that the **ATP/ADP carrier**, along with the plant uncoupling mitochondrial protein, participates in the protonophoric action of palmitate in potato tuber mitochondria.

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ACCESSION NUMBER: 95353300 EMBASE
 DOCUMENT NUMBER: 1995353300
 TITLE: Developmental changes of the adenine nucleotide translocation in rat brain.
 AUTHOR: Schonfeld P.; Bohnensack R.
 CORPORATE SOURCE: Institut fur Biochemie, Medizinisch Fakultat, Otto-von-Guericke-Univ. Magdeburg, Leipziger Str. 44,39120 Magdeburg, Germany
 SOURCE: Biochimica et Biophysica Acta - Bioenergetics, (1995) 1232/1-2 (75-80).
 ISSN: 0005-2728 CODEN: BBBEB4
 COUNTRY: Netherlands
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 002 Physiology
 008 Neurology and Neurosurgery
 029 Clinical Biochemistry
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB The perinatal development of the adenine nucleotide translocation in isolated rat brain mitochondria was studied. For that purpose the content of the adenine nucleotide translocase (**ANT**), the activity of adenine nucleotide translocation and the control of the **ANT** protein over State 3 respiration were estimated. From the newborn to the adult state there was a 4-fold increase in State 3 respiration which was paralleled by a 3-fold increase in the respiratory control ratio. The capacity of uncoupled respiration exceeded that of State 3 respiration in all developmental stages indicating that the activity of oxidative phosphorylation is influenced by that of **ANT** and/or ATP synthase. The content of the **ANT** protein, measured as bound pmoles of [3H]atractyloside per mg mitochondrial protein, increased more than 2-fold from birth to adulthood in the first three postnatal weeks. The size of the exchangeable matrix (ATP + ADP)-pool was only slightly expanded during the same period. The translocation activity increased 2-fold from the newborn to the adult state and was a linear function of the **ANT** protein. Control of the **ANT** protein over State 3 respiration (quantified as flux control coefficient, $C(\text{ANT})(J_o)$) was remarkable in brain mitochondria from newborn rats ($C(\text{ANT})(J_o) = 0.45 \pm 0.15$), but declined during further development ($C(\text{ANT})(J_o) = 0.11 \pm 0.03$, at the 20th day). The obtained results suggest that the postnatal enrichment of the **ANT** protein in rat brain mitochondria is an essential factor for the development of oxidative phosphorylation capacity in the early postnatal period.

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ACCESSION NUMBER: 93290277 EMBASE
 DOCUMENT NUMBER: 1993290277
 TITLE: Increase in the adenine nucleotide translocase protein contributes to the perinatal maturation of respiration in rat liver mitochondria.
 AUTHOR: Schonfeld P.; Fritz S.; Halangk W.; Bohnensack R.
 CORPORATE SOURCE: Institut fur Biochemie, Medizinische Akademie, Leipziger Strasse 44,39120 Magdeburg, Germany
 SOURCE: Biochimica et Biophysica Acta - Bioenergetics, (1993) 1144/3 (353-358).
 ISSN: 0005-2728 CODEN: BBBEB4
 COUNTRY: Netherlands
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 021 Developmental Biology and Teratology

029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB An assay based on the high-affinity binding of tritium-labelled **atractyloside** to the adenine nucleotide translocase (**ANT**) was developed for estimation of its content in samples of mitochondria, cells and tissue homogenate. The assay was used to study the developmental change of the **ANT** protein concentration in perinatal rat liver. Within the last 3 days before birth the content of the **ANT** protein per mg tissue protein increased from 29 to 45% of the maximum value found 2 days after birth. A similar developmental change of the **ANT** protein was found in isolated mitochondria, demonstrating that the perinatal increase in the **ANT** protein content was due mainly to a mitochondrial differentiation process and not the result of an increase in the number of mitochondria per cell. A close proportionality between the **ANT** protein and the ADP-stimulated respiration of liver homogenate was found in the perinatal period from 3 days before to 2 days after birth. This finding suggests that the developmental change in the **ANT** protein content plays an important role in the onset of oxidative phosphorylation after birth.

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ACCESSION NUMBER: 88010831 EMBASE

DOCUMENT NUMBER: 1988010831

TITLE: Modulation of adenine nucleotide translocase activity during myocardial ischemia.

AUTHOR: Shug A.L.; Subramanian R.

CORPORATE SOURCE: Department of Neurology, William S. Middleton Memorial Veterans Administration Hospital, Madison, WI, United States

SOURCE: Zeitschrift fur Kardiologie, (1987) 76/SUPPL. 5 (26-33).

ISSN: 0300-5860 CODEN: ZKRDAX

COUNTRY: Germany

DOCUMENT TYPE: Journal

FILE SEGMENT: 002 Physiology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: German; English

AB Preliminary studies have shown that high levels of free fatty acids, which elevate LCACAE and lower levels of free carnitine, are much more harmful to the heart after repeated periods of ischemia and reperfusion than after exposure to continuous ischemia and reperfusion. These observations appear to support our hypothesis that LCACAE inhibition of the mitochondrial **ANT** during ischemia potentiates free radical mediated damage to the inner mitochondrial membrane during reperfusion. These and related findings by others have led us to hypothesize that the mechanisms of ischemic injury to the heart involve the following sequence of events: (1) exposure to high levels of FFA during ischemia and reperfusion results in permanently elevated LCACAE and low free carnitine levels; (2) LCACAE-**ANT** binding increases and **ANT** activity decreases; (3) mitochondrial swelling occurs because of decreased ADP/ATP transport and oxidative phosphorylation; (4) complex III activity is altered (superoxide formation increases), and swelling of mitochondrial membranes exposes C = C bonds that are required for lipid peroxidation, which can lead to inner mitochondrial membrane damage. We further hypothesize that LCACAE-**ANT** inhibition-induced free radical damage causes the loss of mitochondrial matrix components (22), eventually leading to lesions of the

sarcolemmal membrane and cell necrosis (22). Studies now in progress support this hypothesis and indicate that inhibition of **ANT** in isolated rat heart mitochondria by **carboxyatractyloside** or palmitoyl CoA stimulates free radical formation, probably at the complex III loci. Stimulation of free radical formation by palmitoyl CoA was reversed by L-carnitine. These findings, if substantiated by further studies, may provide the first evidence that L-carnitine protects the ischemic heart from free radical damage.

=> d iall abeq tech abex 42-

YOU HAVE REQUESTED DATA FROM 5 ANSWERS - CONTINUE? Y/(N):y

L36 ANSWER 42 OF 46 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-552661 [53] WPIX
 CROSS REFERENCE: 2001-291054 [30]
 DOC. NO. CPI: C2004-202272
 TITLE: Novel nucleic acid expression construct having a polynucleotide encoding mitochondrial permeability transition pore component polypeptide, useful in identifying agents altering mitochondrial permeability transition.
 DERWENT CLASS: B04 D16
 INVENTOR(S): ANDREYEV, A Y; CLEVINGER, W; DAVIS, R E; FRIGERI, L G; MURPHY, A N; VELICELEBI, G; WILEY, S E
 PATENT ASSIGNEE(S): (MITO-N) MITOKOR INC
 COUNTRY COUNT: 1
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2004146892	A1	20040729	(200453)*		67	C12Q001-68	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2004146892	A1 CIP of	US 1999-434354	19991103
	Cont of	US 2000-709785	20001103
		US 2003-684232	20031010

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2004146892	A1 CIP of	US 6562563

PRIORITY APPLN. INFO: US 2000-709785 20001103; US
 1999-434354 19991103; US
 2003-684232 20031010

INT. PATENT CLASSIF.:

MAIN: C12Q001-68
 SECONDARY: C07H021-04

BASIC ABSTRACT:

US2004146892 A UPAB: 20040818
 NOVELTY - A nucleic acid expression construct (I) comprising a promoter operably linked to a polynucleotide encoding a mitochondrial permeability transition (MPT) pore component polypeptide or cyclophilin (Cyp) polypeptide fused to an energy transfer molecule polypeptide or its variant, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

- (1) a polypeptide (II) comprising:
 - (a) MPT pore component polypeptide fused to an energy transfer molecule polypeptide, or its derivative; or
 - (b) Cyp polypeptide fused to an energy transfer molecule polypeptide, or its derivative;
- (2) a host cell (III) for identifying agents that alter MPT, comprising a first nucleic acid expression construct, having a promoter operably linked to a polynucleotide encoding a MPT pore component polypeptide fused to a polynucleotide encoding a first energy transfer molecule or its variant, and a second nucleic acid expression construct comprising a promoter operably linked to a polynucleotide encoding a Cyp polypeptide fused to a polynucleotide encoding a second energy transfer molecule or its variant, where binding of MPT pore component polypeptide to the Cyp polypeptide results in detectable energy transfer between the first and second energy transfer molecules;
- (3) detecting (M1) an agent that alters MPT, involves contacting a CypD polypeptide with an adenine nucleotide translocator (**ANT**) polypeptide and a candidate agent, under conditions and for a time sufficient to permit the CypD, **ANT**, and the candidate agent to interact, and detecting a level of binding of CypD polypeptide to **ANT** polypeptide, relative to a level of binding detected in the absence of the candidate agent, and thus detecting an agent that alters MPT;
- (4) an agent (A1) capable of altering MPT, where the agent is identified by using (III) or (M1); and
- (5) a kit (K1) for screening for agents that alter MPT, comprising:
 - (a) an isolated CypD polypeptide or its derivative, an isolated **ANT** polypeptide or its derivative, and a detection reagent that specifically binds to at least one of the polypeptides; or
 - (b) a host cell, a first nucleic acid expression construct as mentioned above, and a second nucleic acid expression construct as mentioned above.

ACTIVITY - Nootropic; Neuroprotective; Antiparkinsonian; Antidiabetic; Cytostatic; Antipsoriatic; Neuroleptic; Anticonvulsant; Cerebroprotective; Vasotropic.

No biological data given.

MECHANISM OF ACTION - Alters MPT (claimed).

USE - (I) is useful in detecting an agent that alters MPT. (III) is useful for screening an agent that alters MPT, which involves contacting (III) having a mitochondrion with a candidate agent and an inducer of MPT, exposing the cell to an excitation energy, detecting a level of energy transfer between the first and second energy transfer molecules, and comparing the level of energy transfer to a first reference level generation in the absence of candidate agent, and thus identifying an agent that alters MPT. The host cell is further contacted with an inhibitor of MPT to generate a second reference level. The inhibitor of MPT is chosen from low pH, inducers of high mitochondrial membrane potential, and Cyp A. The inducer of MPT is **atractyloside** or **bonkreikic acid**. The inducer of MPT comprises a compound that increases Ca^{2+} concentration in the mitochondria. The candidate agent increases or decreases energy transfer between the first and second energy transfer molecules. The excitation energy is light with a wavelength ranging from 300-650 nm. The first or second energy transfer molecule has an excitation maximum at a wavelength ranging from 400-500 nm, preferably 433 nm, and an emission maximum at a wavelength ranging from 450-525 nm, preferably 475 nm, and the second energy transfer molecule has an excitation maximum at a wavelength ranging from 450-525 nm, preferably 513 nm, and an emission maximum at a wavelength ranging from 500-550 nm, preferably 527 nm, or the second energy transfer molecule has an excitation maximum at a wavelength

ranging from 400-450 nm, preferably 433 nm, and an emission maximum at a wavelength ranging from 450-500 nm, preferably 475 nm, and the first energy transfer molecule has an excitation maximum at a wavelength ranging from 500-525 nm, preferably 513 nm, and an emission maximum at a wavelength ranging from 525-550 nm, preferably 527 nm. (III) is useful for preparing a MPT pore component polypeptide or a Cyp polypeptide, which involves culturing (III), under conditions that permit expression of the fusion protein, and recovering fusion protein from the culture. The fusion protein comprises a recognition sequence for a protease or a ligand for a receptor. A1 is useful for altering survival of a cell, which involves contacting a cell with A1, under conditions and for a time sufficient to modulate cell survival. A1 is useful for altering MPT, which involves contacting a mitochondrion with A1, under conditions and for a time sufficient to alter MPT. The mitochondrion is present within a cell, which is present within a living organism. The cell is a hybrid cell (claimed).

The **ANT** and CypD polypeptides, such as fusion proteins are useful within intact cells, or in preparation of intact organelles such as mitochondria, cell membranes or intracellular vesicles. The polypeptides are useful in disrupted cell preparations, including cell homogenates or lysates. A1 is useful for treating or preventing diseases associated with the altered mitochondrial function, where the diseases are chosen from Alzheimer's disease, diabetes mellitus, Parkinson's disease, Huntington's disease, schizophrenia, stroke, cancer and psoriasis.

Dwg.0/15

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; DCN
 MANUAL CODES: CPI: B04-B04C; B04-E02F; B04-E03F; B04-E08; B04-F0100E;
 B04-G01; B04-K0100E; B04-N02A0E; B11-C08E;
 B11-C08F2; B11-C08F4; B11-C10; B12-K04E; B12-K04F;
 B14-F01E; B14-H01B; B14-J01A3; B14-J01A4; B14-J01B3;
 B14-J07; B14-L01; B14-L06; B14-N17C; B14-S03;
 B14-S04; D05-H07; D05-H08; D05-H09; D05-H11;
 D05-H12A; D05-H12E; D05-H14; D05-H17A6; D05-H18

TECH UPTX: 20040818

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Construct: In (I), the MPT pore component is **ANT**. The **ANT** is chosen from human ANT1, human ANT2 and human ANT3. MPT pore component is chosen from porin, hexokinase, creatine kinase, peripheral benzodiazepine receptor-associated protein (PRAX), calcium modulating cyclophilin ligand (CAML) and the peripheral benzodiazepine receptor. The Cyp is CypD. The Cyp is chosen from human Cyp A, Cyp B, human Cyp C and human Cyp-60. (I) comprises a vector chosen from plasmids, cosmids, shuttle vectors, viral vectors and vectors comprising chromosomal origin of replication. The vector comprises a plasmid chosen from pBAD-His, pEYFP-C1 and pECFP-N1. The promoter is externally regulated. The energy transfer molecule is chosen from green fluorescent protein (GFP), a fluorescein arsenical helix binder (FLASH) sequence and an aequorin protein. The GFP is chosen from blue-shifted GFP, cyan-shifted GFP, red-shifted GFP and yellow-shifted GFP. The energy transfer molecule is a derivative of an energy transfer molecule chosen from GFP, FLASH sequence and aequorin protein.

Preferred Host cell: (III) is eukaryotic cell chosen from 293, COS-1, Sf9, Chinese hamster ovarian cells (CHO), Hep-2, Madin-Darby canine kidney cells (MDCK) and Jurkat. The first and second energy transfer molecules are chosen from GFP, blue-shifted GFP, cyan-shifted GFP, red-shifted GFP and yellow-shifted GFP. The first and second energy transfer molecules have an excitation maximum at a wavelength ranging from 300-650 nm and an emission maximum at a wavelength ranging from 350-675 nm. The first energy transfer molecule and the second energy transfer molecule have excitation and emission maxima at different wavelengths. The one or more nucleic acid expression construct is extrachromosomal or is integrated into a host cell

chromosome, where chromosome is a mitochondrial chromosome.
 Preferred Method: In (M1), the CypD polypeptide is immobilized on a support, and is a fusion protein. The **ANT** polypeptide is immobilized on a support, and is a fusion protein, where the fusion protein comprises a protease recognition sequence or ligand for a receptor. The candidate agent is chosen from peptides, polypeptides, proteins and small molecules, preferably small molecule present within a combinatorial library.

Preferred Kit; In K1, the detection reagent is an antibody or its antigen-binding fragment.

ABEX UPTX: 20040818

ADMINISTRATION - A1 is administered by oral, topical, parenteral including intravenous, subcutaneous, intramuscular, intrasternal or intrathecal, sublingual, rectal, vaginal or intranasal route.

No specific dosage details are given.

EXAMPLE - Total cellular RNA prepared from whole human brain was obtained. The RNA was purified by treatment with RNase-free DNaseI, using 1 microl of DNaseI (10 U/microl) in buffer containing 40 mM Tris-hydrochloric acid, pH 7.0, 6 mM magnesium chloride, and 2 mM calcium chloride for 30 minutes at 37 degreesC. The treatment was followed by two phenol/chloroform extractions, one chloroform extraction, and an ethanol precipitation in the presence of sodium acetate. The RNA pellet was collected by centrifugation, washed with 70% ethanol, air-dried and resuspended in RNase-free sterile water. The RNA was reverse transcribed to generate cDNA. The adenine nucleotide translocator (**ANT**) cDNA was amplified by PCR, using primers having sequences such as 5'-ttatatctcgagtatgggtgatcacgcttggagcttcctaaag-3' and 5'-tatataggtaccttagacatatttttgatctcatcataaac-3'. The PCR products were digested with restriction enzymes such as XhoI and Asp718. The restricted **ANT** cDNAs were ligated with expression vector such as pBAD/His. Thus, an expression construct comprising mitochondrial permeability transition pore component polypeptide such as **ANT** was prepared.

L36 ANSWER 43 OF 46 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2002-383045 [41] WPIX
 DOC. NO. CPI: C2002-107929
 TITLE: Preventing human immunodeficiency virus-1 viral protein R-adenine nucleotide translocator interaction, useful to prevent channel formation in mitochondrial membranes.
 DERWENT CLASS: B04 D16
 INVENTOR(S): BELZACQ, A; BRENNER-JAN, C; EDELMAN, L; HOEBEKE, J; JACOTOT, E D F; KROEMER, G; ROQUES, B P; EDELMANN, L
 PATENT ASSIGNEE(S): (CNRS) CENT NAT RECH SCI; (INRM) INSERM INST NAT SANTE & RECH MEDICALE; (INSP) INST PASTEUR; (UYCO-N) UNIV COMPIEGNE; (CNRS) CNRS CENT NAT RECH SCI; (BELZ-I) BELZACQ A; (BREN-I) BRENNER-JAN C; (EDEL-I) EDELMAN L; (HOEB-I) HOEBEKE J; (JACO-I) JACOTOT E D F; (KROE-I) KROEMER G; (ROQU-I) ROQUES B P; (EDEL-I) EDELMANN L
 COUNTRY COUNT: 97
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2002020570	A2	20020314	(200241)*	EN	65	C07K014-155	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ							
NL OA PT SD SE SL SZ TR TZ UG ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ							
LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU							

SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
 US 2002068273 A1 20020606 (200241) C12Q001-70
 AU 2002015004 A 20020322 (200251) C07K014-155
 EP 1370572 A2 20031217 (200402) EN C07K007-08
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR
 JP 2004508385 W 20040318 (200420) 110 C07K014-47
 US 2004072146 A1 20040415 (200426) C12Q001-70

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002020570	A2	WO 2001-EP11316	20010911
US 2002068273	A1 Provisional	US 2000-231539P	20000911
	Provisional	US 2000-232841P	20000915
		US 2001-949650	20010912
AU 2002015004	A	AU 2002-15004	20010911
EP 1370572	A2	EP 2001-983518	20010911
		WO 2001-EP11316	20010911
JP 2004508385	W	WO 2001-EP11316	20010911
		JP 2002-525189	20010911
US 2004072146	A1 Provisional	US 2000-231539P	20000911
	Provisional	US 2000-232841P	20000915
	Cont of	WO 2001-EP11316	20010911
		US 2003-383592	20030310

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002015004	A Based on	WO 2002020570
EP 1370572	A2 Based on	WO 2002020570
JP 2004508385	W Based on	WO 2002020570

PRIORITY APPLN. INFO: US 2000-232841P 20000915; US
 2000-231539P 20000911; US
 2001-949650 20010912; US
 2003-383592 20030310

INT. PATENT CLASSIF.:

MAIN: C07K007-08; C07K014-155; C07K014-47; C12Q001-70
 SECONDARY: A61K038-00; A61K039-395; A61K039-42; A61K045-00;
 A61P043-00; C12P019-34; C12Q001-02; G01N033-15;
 G01N033-50; G01N033-569; G01N033-68

BASIC ABSTRACT:

WO 200220570 A UPAB: 20020701
 NOVELTY - Preventing (M1) interaction of human immunodeficiency virus (HIV)-1 viral protein R (Vpr) with adenine nucleotide translocator (ANT), comprising providing a molecule capable of preventing the binding of full-length Vpr to ANT, and contacting the molecule with an ANT fragment, where the molecule prevents the interaction of the ANT fragment with Vpr, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) screening (M2) for molecules that compete with the binding of the C-terminal moiety of Vpr to ANT, comprising:

(a) providing a Vpr fragment capable of binding to ANT;

(b) contacting the Vpr fragment with an ANT fragment capable of binding to Vpr in the presence and absence of a test molecule; and

(c) detecting the binding of the Vpr fragment to the **ANT** fragment in the presence and absence of a test molecule;

(2) screening for molecules that mimic Vpr or Vpr fragments in its capacity to interact physically with **ANT**, comprising:

(a) providing a Vpr or Vpr fragment capable of interacting with **ANT**;

(b) contacting the Vpr or its fragment with an **ANT** fragment capable of interacting with Vpr or its fragment in the presence or absence of a test molecule; and

(c) detecting the binding of the Vpr or Vpr fragment to the **ANT** fragment in the presence or absence of a test molecule;

(3) a peptidic or non-peptidic molecule (I) that prevents or causes permeabilization of mitochondrial membranes, where the molecule prevents or enhances the binding of Vpr to **ANT**;

(4) a pharmaceutical and diagnostic composition (C) comprising (I);

(5) screening for genetic or epigenetic alterations in the expression or structure of the three **ANT** isoforms in humans, comprising:

(a) providing a fragment of Vpr, where the fragment is capable of binding to **ANT**, with a sample comprising human **ANT**;

(b) mixing the fragment with a biological and control samples comprising human **ANT**;

(c) detecting the binding of Vpr to **ANT** in the biological sample and the control sample;

(d) correlating a difference in binding with a genetic or epigenetic alteration of **ANT**; and

(e) optionally detecting a difference in the **ANT** capacity to form channel in liposome or in planar lipids bilayers;

(6) quantifying the level of the three human **ANT** isoforms in a cell, by mixing Vpr with a biological sample comprising **ANT** in an amount effective to bind to **ANT**, and quantitating the level of binding of Vpr to **ANT**;

(7) screening (M3) active molecules of interest that induce to prevent formation of a lethal pore by **ANT**, comprising:

(a) providing purified **ANT** in artificial lipid bilayers or liposomes;

(b) contacting molecules of interest to be screened with the **ANT**; and

(c) detecting lethal pore formation by measuring the release of labeled substrate;

(8) screening active molecules of interest that inhibit the formation of a lethal pore without preventing antiport function, comprising:

(a) providing a composition comprising purified **ANT** in artificial lipid bilayers or liposomes with a molecule that induces the formation of a lethal pore;

(b) contacting the composition in the presence or absence of a test molecule;

(c) detecting by fluorescence the presence of the antiport function; and

(d) detecting by another fluorescence the test molecule that inhibits the formation of a lethal pore; and

(9) an isolated or purified peptide having the sequence (S1).

(S1) is Asp-Arg-His-Lys-Gln-Phe-Trp-Arg-Tyr-Phe-Ala-Gly-Asn.

ACTIVITY - None given.

MECHANISM OF ACTION - Modulator of physical and functional interaction between Vpr and **ANT**; modulator of mitochondrial membrane permeabilization (claimed).

No biological data is given.

USE - M1 is useful for preventing channel formation in mitochondrial membranes and permeabilization of mitochondrial membranes. M1 is also useful for preventing cell death by apoptosis. (C) is useful for causing

or preventing permeabilization of mitochondrial membranes. (All claimed).
Dwg.0/9

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B04-C01C; B04-N03; B04-N04; B09-C02; B10-B01B;
B10-D03; B10-E04C; B11-C07B; B12-K04E; D05-H09

TECH UPTX: 20020701

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The molecule in M1, is Bcl-2 or its fragment. The Vpr fragment comprises full length Vpr, or amino acids 52-96 of HIV-1 Vpr. The active molecule that induces the formation of a lethal pore is Vpr, its fragment or variant. Alternatively, the active molecule is **atractyloside**, mastoparan, terbutyl, diamide or pro-apoptotic molecules of Bcl-2 family e.g. a BAX molecule.

ABEX UPTX: 20020701

WIDER DISCLOSURE - (1) structural or functional inhibitors effective in blocking Vpr/**ANT** interaction or Vpr/voltage-dependent anion channel (VDAC) interaction;

(2) screening agonist or antagonist of **ANT**;

(3) variants of Vpr or **ANT** that are altered in their binding activity;

(4) antigenic epitopes of (I);

(5) antibodies to (I); and

(6) conjugates comprising (I).

ADMINISTRATION - (C) is administered through topical or parenteral route, or by inhalation. No dosage is given.

L36 ANSWER 44 OF 46 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 2004-133275 [14] WPIX

CROSS REFERENCE: 2000-365619 [31]

DOC. NO. NON-CPI: N2004-106447

DOC. NO. CPI: C2004-053225

TITLE: Novel recombinant expression construct comprising regulated promoter linked to nucleic acid encoding adenine nucleotide translocator polypeptide, useful for screening compound interacting with polypeptide.

DERWENT CLASS: B02 B04 D16 J04 K08 S03

INVENTOR(S): ANDERSON, C M; CLEVENGER, W; DAVIS, R E; GHOSH, S S;
MILLER, S W; SZABO, T R; WILEY, S E

PATENT ASSIGNEE(S): (MITO-N) MITOKOR

COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
AU 2002029270	A	20020523	(200414)*		177	C07K014-47	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
AU 2002029270	A Div ex	AU 2000-24729	19991103
		AU 2002-29270	20020328

PRIORITY APPLN. INFO: AU 2000-24729 19991103; AU
2002-29270 20020328

INT. PATENT CLASSIF.:

MAIN: C07K014-47
SECONDARY: C12N005-10; C12N009-00; C12N015-12; C12N015-62;

C12N015-86; G01N033-50

BASIC ABSTRACT:

AU 200229270 A UPAB: 20040226

NOVELTY - A recombinant expression construct (I) comprising regulated promoter operably linked to first nucleic acid (N1) encoding adenine nucleotide translocator (**ANT**) polypeptide, or promoter operably linked to nucleic acid molecule comprising N1 and a second nucleic acid sequence (N2), where animal **ANT** polypeptide is expressed as fusion protein with polypeptide product of N2, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) a host cell (II) comprising (I);
- (2) producing (M1) a recombinant **ANT** polypeptide, involves culturing (II) infected with (I), which is a recombinant viral expression construct;
- (3) an **ANT** polypeptide produced by (M1);
- (4) an isolated human **ANT** polypeptide (III);
- (5) an isolated human **ANT** fusion protein (IV) comprising an **ANT** polypeptide fused to one or more additional polypeptide sequences, where the sequences are cleavable by a protease and the **ANT** polypeptide are separable from (IV) by cleavage with protease;
- (6) an isolated **ANT** fusion protein comprising first polypeptide that is an animal **ANT** polypeptide fused to an additional polypeptide sequence;
- (7) an isolated recombinant animal **ANT** fusion protein, comprising an **ANT** polypeptide fused to an additional polypeptide sequence cleavable by a protease;
- (8) identifying an agent that binds to **ANT** polypeptide, involves contacting a candidate agent with a biological sample containing recombinant **ANT** polypeptide under conditions and for a time sufficient to permit binding of the agent to the recombinant **ANT** polypeptide and detecting binding of the agent to the recombinant **ANT** polypeptide;
- (9) an **ANT** ligand comprising **atractyloside** substituted at the 6' hydroxyl to form an **atractyloside** derivative, where the ligand has a structural formula (V), its stereoisomers and salts;
- (10) an assay plate for high throughput screening of candidate agents that bind to an **ANT** polypeptide, comprising an assay plate having several wells, where each of the wells further comprises an immobilized recombinant **ANT** polypeptide, its variant or fragment;
- (11) targeting a polypeptide of interest to a mitochondrial membrane, involves expressing (I) encoding a fusion protein in a host cell, where the construct comprises promoter of (I) and a second nucleic acid sequence encodes the polypeptide of interest; and
- (12) a pharmaceutical composition (VI) comprising (V), or an agent that binds to **ANT** polypeptide or interacts with **ANT** polypeptide;
- (13) a method (VII) for identifying an agent that binds to an **ANT** polypeptide, which involves contacting a candidate agent with (II) expressing a recombinant **ANT** polypeptide under conditions and for a time sufficient to permit binding of the agent to the recombinant **ANT** polypeptide and detecting binding of the agent to the recombinant **ANT**;
- (14) a method (VIII) for determining the presence of an **ANT** polypeptide in a biological sample, which involves contacting a biological sample suspected of containing an **ANT** polypeptide with (V) under conditions and for a time sufficient to allow binding of (V) to an **ANT** polypeptide, and detecting the binding of (V) to an

ANT polypeptide;

(15) a method for identifying an agent that interacts with an **ANT** polypeptide, which involves contacting a biological sample containing recombinant **ANT** with a detectable (V) in the presence of a candidate agent, and comparing binding of the detectable (V) to recombinant **ANT** in the absence of the agent to binding of the detectable (V) to recombinant **ANT** in the presence of the agent.

R1 = hydroxyl, halogen, -OC(=O)R4 or -NHR4;

R2 = hydrogen or -C(=O)R5;

R3 = -CH3 or =CH2;

R4 = -X-aryl, -X-substituted aryl, -X-arylalkyl, -X-substituted arylalkyl, -X-heteroaryl, or -X-heteroarylalkyl;

X = optional amido or alkylamido linker moiety; and

R5 = alkyl.

ACTIVITY - None given.

MECHANISM OF ACTION - Regulator of adenine nucleotide translocator function.

No supporting data is given.

USE - (II) is useful for identifying an agent that binds to an **ANT** polypeptide. (V) is useful for determining the presence of an **ANT** polypeptide in a biological sample. (V) is useful for isolating **ANT** from a biological sample, which involves carrying out the above mentioned contacting step, and recovering the **ANT** polypeptide, where (V) is covalently or non-covalently bound to a solid phase. (V) is also useful for identifying an agent that interacts with an **ANT** polypeptide. (VI) is useful for treating a subject, which involves administering (VI) to the subject (all claimed).

(I) is useful for screening compounds interacting with **ANT**.

DESCRIPTION OF DRAWING(S) - The figure shows a graph representing the binding of (32P) ATP to Sf9/human adenine nucleotide translocator3 mitochondria.

Dwg.7/19

FILE SEGMENT: CPI EPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B04-C01; B04-E02F; B04-E03F; B04-E04; B04-E08;
B04-F0100E; B04-F0200E; B04-F10A3E; B04-N0400E;
B04-N04A; B04-P0100E; B11-C07B5; B11-C08E3;
B11-C08E4; B11-C08E5; B11-C10A; B12-K04E; B12-K04F;
D05-A02C; D05-H09; D05-H12E; D05-H14; D05-H17B6;
J04-B01; K08-X; K09-B

EPI: S03-E14H

TECH UPTX: 20040226

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Expression Construct: (I) further comprises an additional nucleic acid sequence that regulates transcription, where the additional nucleic acid sequence encodes a repressor of the regulated promoter. The **ANT** polypeptide comprises a human **ANT** polypeptide such as ANT1, ANT2 or ANT3.

The **ANT** polypeptide is expressed as a fusion protein with a product of a second nucleic acid sequence encoding a polypeptide cleavable by a protease, where the polypeptide product is an enzyme and the **ANT** polypeptide is separable from the fusion protein by cleavage with protease. The fusion protein localizes to membranes such as mitochondrial membranes.

Preferred Polypeptide: (III) is recombinant ANT1, ANT2, ANT3, its variant or fragments.

Preferred Fusion Protein: In (IV), additional polypeptide sequence is an enzyme sequence, its variant or fragment. The additional polypeptide sequence is a polypeptide having a sequence of affinity for a ligand.

Preferred **ANT** Ligand: In (V), R1 is preferably hydroxyl, -OC(=O)R4 or -NHR4, R4 is preferably -X-aryl, -X-substituted aryl,

-X-arylalkyl, or -X-substituted arylalkyl. R5 is preferably CH₂CH(CH₃)₂. Preferred Method: In the method of (VII), (II) is derived from Escherichia coli cell, yeast cell, an insect cell or a mammalian cell. The insect cell is chosen from an Sf9 cell and a Trichoplusia ni cell. (II) lacks one or more isoforms of an endogenous **ANT**. The expression of one or more genes encoding an endogenous **ANT** isoform is substantially impaired.

In the method of (VIII), the detectable **atractyloside** derivative comprises radiolabeled substituent, fluorescent substituent or covalently bound biotin. The radiolabeled substituent is chosen from 125I, 131I, 3H, 14C and 35S, where (V) further comprises a Eu³⁺ atom complexed to the **atractyloside** derivative. The **atractyloside** molecule is substituted at 6' hydroxyl with an amine or an amine containing functionality to form an amine modified **atractyloside** derivative. The **atractyloside** molecule is a **carboxyatractyloside** molecule that is substituted at 6' hydroxyl to form an **atractyloside** derivative that is a **carboxyatractyloside** derivative.

ABEX

UPTX: 20040226

WIDER DISCLOSURE - Antisense nucleotides and triplex molecules complementary to or bind the sense strand of DNA or mRNA that encodes **ANT** polypeptide is also disclosed.

ADMINISTRATION - (VI) is administered orally, topically, sublingually, buccally, rectally, vaginally, intranasally, subcutaneously, intravenously, intramuscularly, or intrasternally. No specific dosage details are given.

EXAMPLE - Total cellular RNA prepared from whole human brain was obtained commercially. The RNA was purified by treatment with RNase-free DNaseI using 1 ul of DNaseI (10 u/ul) in a buffer containing 40 mM tris-hydrochloric acid (pH 7.0), 6 mM magnesium chloride and 2 mM calcium chloride for 30 minutes at 37 degreesC. The treatment was followed by two phenol/chloroform extractions, one chloroform extraction and an ethanol precipitation in the presence of sodium acetate. The RNA pellet was collected by centrifugation, washed with 70% ethanol, air dried and resuspended in RNase-free sterile water. The RNA was reverse transcribed to generate cDNA. Adenine nucleotide translocator (**ANT**) cDNAs were amplified by PCR using primers having sequences of 5'-TTATATCTCGAGTATGGGTGATCAGCTTGGAGCTTCCTAAAG-3' and 5'-TATATAGGTACCTTAGACATATTTTTTGATCTCATCATAACAAC-3. The polymerase chain reaction (PCR) products were digested with restriction endonuclease such as XhoI. The restricted DNAs were purified by horizontal agarose gel electrophoresis. The plasmid pBAD/His DNA was prepared by digestion with the restriction endonuclease such as XhoI. The restricted **ANT** cDNA was ligated with linearized plasmid using DNA ligase. The prepared mixture was then introduced into Escherichia coli TOP10F strain. Colonies were selected and grown in 3-5 ml of LB broth containing 50 mug/ml of ampicillin. The plasmid DNA was isolated from the bacterial culture. The presence of recombinant human **ANT** nucleotide sequences present in the expression constructs was determined. Thus, a recombinant expression vector comprising nucleic acid encoding **ANT** polypeptide was prepared.

L36 ANSWER 45 OF 46 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-291054 [30] WPIX
CROSS REFERENCE: 2004-552661 [53]
DOC. NO. CPI: C2001-089349
TITLE: New nucleic acid expression constructs, useful for screening for agents that alter mitochondrial

permeability transition (MPT), comprises polynucleotide encoding MPT polypeptide or cyclophilin polypeptide fused to energy transfer molecule.

DERWENT CLASS:

B04 D16

INVENTOR(S):

ANDREYEV, A Y; CLEVINGER, W; DAVIS, R E; FRIGERI, L G; MURPHY, A N; VELICELEBI, G; WILEY, S E; VELECELEBI, G

PATENT ASSIGNEE(S):

(MITO-N) MITOKOR

COUNTRY COUNT:

95

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2001032876	A2	20010510	(200130)*	EN	154	C12N015-12	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ							
NL OA PT SD SE SL SZ TR TZ UG ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM							
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC							
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE							
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW							
AU 2001013622	A	20010514	(200149)			C12N015-12	
EP 1228206	A2	20020807	(200259)	EN		C12N015-12	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT							
RO SE SI TR							
JP 2003516128	W	20030513	(200334)		216	C12N015-09	
US 6562563	B1	20030513	(200335)			C12N005-00	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001032876	A2	WO 2000-US30535	20001103
AU 2001013622	A	AU 2001-13622	20001103
EP 1228206	A2	EP 2000-975595	20001103
		WO 2000-US30535	20001103
JP 2003516128	W	WO 2000-US30535	20001103
		JP 2001-535558	20001103
US 6562563	B1	US 1999-434354	19991103

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001013622	A Based on	WO 2001032876
EP 1228206	A2 Based on	WO 2001032876
JP 2003516128	W Based on	WO 2001032876

PRIORITY APPLN. INFO: US 1999-434354 19991103

INT. PATENT CLASSIF.:

MAIN: C12N005-00; C12N015-09; C12N015-12

SECONDARY: C07K014-435; C07K014-47; C07K019-00; C12N001-15; C12N001-19; C12N001-21; C12N005-10; C12N009-90; C12N015-61; C12N015-62; C12P021-02; C12Q001-00; C12Q001-02; C12Q001-32; C12Q001-48; C12Q001-54; G01N033-15; G01N033-50; G01N033-53; G01N033-533; G01N033-566; G01N033-68

BASIC ABSTRACT:

WO 200132876 A UPAB: 20040818

NOVELTY - A nucleic acid expression construct (I) comprising a promoter operably linked to a polynucleotide encoding a mitochondrial permeability transition (MPT) pore component polypeptide fused to an energy transfer

molecule (ETM) polypeptide or its variant, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) a nucleic acid expression construct (II) comprising a promoter operably linked to a polynucleotide encoding a cyclophilin (Cyp) polypeptide fused to an ETM polypeptide or its variant;
- (2) a polypeptide (III) comprising a MPT pore component polypeptide fused to an ETM polypeptide or its derivative;
- (3) a polypeptide (IV) comprising a Cyp polypeptide fused to an ETM polypeptide or its derivative;
- (4) a host cell (V) for identifying agents that alter MPT comprising (I) and (II), where binding of the MPT pore component to the Cyp polypeptide results in detectable energy transfer between the first and second ETM;
- (5) screening (M1) for an agent that alters MPT comprising:
 - (a) contacting (V) containing a mitochondrion with a candidate agent and an inducer of MPT;
 - (b) exposing (V) to an excitation energy;
 - (c) detecting a level of energy transfer between the first and second ETM; and
 - (d) comparing the level of energy transfer to a first reference level generated in the absence of candidate agent and identifying an agent that alters MPT;
- (6) detecting (M2) an agent that alters MPT comprising:
 - (a) contacting a CypD polypeptide with an **ANT** polypeptide and a candidate agent; and
 - (b) detecting a level of binding of CypD polypeptide to **ANT** polypeptide, relative to a level of binding detected in the absence of the candidate agent;
- (7) an agent (VI) capable of altering MPT identified by M2;
- (8) altering survival of a cell comprising contacting a cell with (VI);
- (9) altering (M3) MPT comprising contacting a cell with (VI);
- (10) preparing (III) or (IV) comprising culturing a host cell containing (I) or (II) respectively and recovering (III) or (IV) from the culture;
- (11) a kit (VII) for screening for agents that alter MPT comprising:
 - (a) an isolated CypD polypeptide or its derivative;
 - (b) an isolated **ANT** polypeptide or its derivative; and
 - (c) a detection reagent that specifically binds to (a) or (b); and
- (12) a kit (VIII) for screening for agents that alter MPT comprising a host cell, (I) and (II).

ACTIVITY - Neuroprotective; nootropic; antidiabetic; antiparkinsonian; ophthalmological; antipsychotic; cerebroprotective; cytostatic; antipsoriatic; auditory; anticonvulsant. No supporting data is given.

MECHANISM OF ACTION - Alter mitochondrial membrane permeability transition; alter interaction between mitochondrial adenine nucleotide translocator and cyclophilin D.

USE - The methods are useful for screening for agents that alter MPT and/or cell survival (claimed). These agents (VI) are useful for the prevention or treatment of diseases associated with altered mitochondrial function or dysfunctional cell survival, such as Alzheimer's disease, diabetes mellitus, Parkinson's disease, Huntington's disease, dystonia, Leber's hereditary optic neuropathy, schizophrenia, mitochondrial encephalopathy, lactic acidosis, stroke, cancer, psoriasis, hyperproliferative disorders, mitochondrial diabetes, deafness and myoclonic epilepsy ragged red fiber syndrome.

Dwg.0/14

FILE SEGMENT:

CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B04-E08; B04-F0100E; B04-G01; B04-N0200E; B11-C07A;
B11-C07B3; B12-K04A; B14-F02D1; B14-H01; B14-J01A3;
B14-J01A4; B14-J01B3; B14-N02; B14-N03; B14-N17C;
B14-S04; D05-H09; D05-H11; D05-H12E; D05-H14;
D05-H17C

TECH UPTX: 20010603

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Component: The MPT pore component is an adenine nucleotide translocator (**ANT**) (preferably human ANT1, human ANT2 or human ANT3), porin, hexokinase, creatine kinase, PRAX, CAML or the peripheral benzodiazepine receptor. Preferred Polypeptide: The Cyp is CypD, human CypA, CypB, human CypC or human Cyp-60. Preferred Molecule: The ETM is a (derivative of a) green fluorescent protein (GFP) (e.g. blue-shifted GFP, cyan-shifted GFP, red-shifted GFP and yellow-shifted GFP), a FLASH sequence or an aequorin protein. Preferred Construct: (I) is a plasmid (e.g. pBAD-His, pEYFP-C1 and pECFP-N1), a cosmid, a shuttle vector, a viral vector or a vector containing a chromosomal origin of replication. The promoter is externally regulated. Preferred Cell: (V) is a prokaryotic or eukaryotic cell, such as 293, COS-7, Sf9, Chinese Hamster Ovary (CHO), Hep-2, MDCK (undefined) or Jurkat. The first and second ETM have an excitation maximum of 300-650 nm and an emission maximum of 350-675 nm. The first and second ETM have excitation and emission maxima at different wavelengths. At least one nucleic acid construct is extrachromosomal or integrated into the host cell mitochondrial chromosome. Preferred Method: M1 further comprises contacting (V) with an inhibitor of MPT (e.g. low pH, inducers of mitochondrial membrane potential and cyclosporin A) to generate a second reference level. Preferably (V) is contacted with **atractyloside** or bongkrekic acid or a compound that increases Ca²⁺ concentration in the mitochondria (e.g. ionophores, ionomycin, thapsigargin, amino acid transmitters, glutamate, N-methyl-D-aspartic acid, carbachol, apoptogens and inducers of potassium depolarization). (V) is further contacted with an inducer of oxidative stress (e.g. ethacrynic acid, buthionine, sulfoximine, diamide, menadione, t-butyl hydroperoxide, phenyl-arsine oxide and nitric oxide). The candidate agent increases or decreases energy transfer between the first and second ETM. The first ETM has an excitation maximum of 400-500 nm (preferably 433 nm) and an emission maximum of 450-525 nm (preferably 475 nm). The second ETM has an excitation maximum of 450-525 nm (preferably 513 nm) and an emission maximum of 500-550 nm (preferably 527 nm). Alternatively the second ETM has an excitation maximum of 400-450 nm (preferably 433 nm) and an emission maximum of 450-500 nm (preferably 475 nm). The first ETM has an excitation maximum of 500-525 nm (preferably 513 nm) and an emission maximum of 525-550 nm (preferably 527 nm). In M2 CypD and **ANT** polypeptide are immobilized on a support and are fusion proteins. They comprise a protease recognition sequence or a ligand for a receptor. The candidate agent is a (poly)peptide, protein or small molecule present within a combinatorial library. In M3 the mitochondrial is present within a cell or living organism. Preferably the cell is a cybrid cell. Preferred Kit: In (VII) the CypD and **ANT** polypeptide are immobilized on a support. The detection reagent is an antibody or antigen-binding fragment.

ABEX UPTX: 20010603

ADMINISTRATION - 0.01-1 wt% of an MPT-altering agent is administered by oral, topical, parenteral, sublingual, rectal, vaginal or intranasal routes.

EXAMPLE - DNA comprising nucleotide sequences encoding human adenine nucleotide translocator 3 (huANT3) by polymerase chain reaction (PCR) from a whole human brain cDNA library using the sense primers (A) and antisense primers (B):

(A) 5'-TTATAGGATCCATGACGGAACAGGCCATCTCCTTCGCCAAA; and

(B) 5'-TTAAGAATTCTTAGATCACCTTCTTGAGCTCGTCGTACAG.

PCR products were digested with the restriction endonucleases BamHI and EcoRI. The Baculovirus transfer vector pBlueBacHis2 (B version) was prepared by digestion with the same restriction endonucleases and the restricted DNA was subjected to gel electrophoresis and band extraction. The PCR products were ligated with the vector DNA. Competent *Escherichia coli* TOP10F' cells were transformed with the ligation mixture and single colonies were selected for growth. Plasmid DNA was isolated. The recombinant **ANT** gene sequences were determined. To insert sequences encoding the huANT3 protein into the baculovirus genome, insect cells (*Spodoptera frugiperda* Sf9 cells) were co-transfected with the construct pMK4B-huANT3 and linear baculoviral DNA engineered to contain a promoterless 3' fragment of the lacZ gene. Recombinant baculoviruses expressing the functional beta-galactosidase were identified. These viruses were recombinant expression constructs that expressed human ANT3 polypeptide in insect cells.

L36 ANSWER 46 OF 46 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2001-244412 [25] WPIX
 DOC. NO. CPI: C2001-073351
 TITLE: Detecting mitochondrial intermembrane space protein (MISP) translocation, by detecting ligand-MISP fusion polypeptide complex, in extramitochondrial space after adding agent that induces MISP translocation.
 DERWENT CLASS: B04 D16
 INVENTOR(S): ANDREYEV, A Y; MURPHY, A N; WILEY, S E
 PATENT ASSIGNEE(S): (MITO-N) MITOKOR
 COUNTRY COUNT: 94
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2001016373	A2	20010308	(200125)*	EN	70	C12Q001-68	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ							
NL OA PT SD SE SL SZ TZ UG ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM							
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC							
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE							
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW							
AU 2000070837	A	20010326	(200137)			C12Q001-68	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001016373	A2	WO 2000-US23638	20000828
AU 2000070837	A	AU 2000-70837	20000828

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000070837	A Based on	WO 2001016373

PRIORITY APPLN. INFO: US 2000-606370 20000628; US

1999-151231P 19990827; US
1999-169508P 19991207

INT. PATENT CLASSIF.:

MAIN: C12Q001-68

BASIC ABSTRACT:

WO 200116373 A UPAB: 20010508

NOVELTY - Detecting (M1) mitochondrial intermembrane space protein (MISP) translocation, involves detecting complex formed between affinity domain of MISP fusion polypeptide (FP) of mitochondria and a detectable ligand, in extramitochondrial space, after adding an agent (I) which induces MISP translocation. An increased signal from complex corresponds to increasing degree of MISP translocation.

DETAILED DESCRIPTION - Detecting (M1) MISP translocation involves:

(a) contacting a sample comprising a mitochondrion with an agent (I) known or suspected to induce MISP translocation under conditions to induce MISP translocation, where the mitochondrion comprises at least one MISP FP containing at least one MISP domain and at least one affinity domain; and

(b) contacting the sample with a detectable ligand that specifically binds to the affinity domain, so that the detectable ligand binds to the fusion polypeptide in extramitochondrial spaces to form detectable ligand:fusion polypeptide complexes (LFPC), and detecting LFPC.

An increasing signal from the detectable LFPC corresponds to an increasing degree of MISP translocation.

INDEPENDENT CLAIMS are also included for the following:

(1) a nucleic acid expression construct (II) comprising a promoter linked to a polynucleotide encoding an intermembrane space protein fusion polypeptide which comprises a MISP domain and at least one affinity domain;

(2) a host cell (III) comprising (II);

(3) an isolated intermembrane space protein fusion polypeptide (IV) that comprises a MISP domain and an affinity domain;

(4) preparation of (IV);

(5) a composition of matter (V) comprising a containing device appropriate for high through-put screening of agents and compounds and (IV);

(6) screening compounds or agents using (V); and

(7) a mechanism for screening compounds or agents comprising (V).

ACTIVITY - Nootropic; neuroprotective; anti-diabetic; antiparkinsonian; anticonvulsant; neuroleptic; cerebroprotective; cytostatic; antipsoriatic.

MECHANISM OF ACTION - MISP translocation modulator.

SY5Y cells stably expressing hemagglutinin (HA) tagged adenylate kinase were treated with apoptogens such as staurosporine, etoposide, thapsigargin and actinomycin, harvested, and analyzed for cytochrome c and adenylate kinase release from the mitochondria. After the treatment, cells were harvested following trypsinization, pelleted by centrifugation and resuspended in a media containing respiratory substrates and digitonin. Cytosol was separated from pellet (which contained mitochondria, other organelles and plasma membrane) by centrifugation. The supernatant was added with Complete Protease Inhibitors. The pellets were solubilized in PLC lysis buffer with complete protease inhibitors. Proteins in the cytosol and pellet samples were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and analyzed by Western blotting. Membranes were initially probed with an anti-cytochrome c antibody and then sequentially stripped and probed with an anti-HA antibody to detect the HA-adenylate kinase fusion protein, and an anti protein kinase B (PKB) antibody to detect PKB/Akt, a soluble cytosolic marker used to confirm that individual gel lanes had been comparably loaded. With increased time of exposure to the indicated apoptogen, increasing amounts of the two MISP markers, cytochrome c and HA-adenylate

kinase, were detected in the cytosolic fraction. The results of Western blot analysis of cytosolic and pellet fractions from cells that had been exposed to 200 nM staurosporine showed that cytochrome c was detected with increased time of exposure to the apoptogen, but the level of HA-adenylate kinase in the cytosolic fraction did not increase over time.

USE - (M1) is useful for identifying an agent (I) that alters MISP translocation and for identifying a compound that alters the activity of (I) (claimed). The method involves comparing the level of extramitochondrial LFPC detected in a control sample to the sample with a candidate agent. An altered level of signal of detectable LFPC in the sample with the candidate agent, relative to the level of signal of detectable LFPC in the control sample, indicates that the candidate agent is (I).

(I) identified by the above methods may be used for inducing apoptosis, or necrosis. (I) that alters MISP translocation and also inhibit or delay the onset of apoptosis may be used for altering initiation of an apoptotic cascade by a mitochondrion. The agents are useful for treating diseases associated with altered mitochondrion function such as Alzheimer's diseases; diabetes mellitus; Parkinson's diseases; Huntingtons's disease; dystonia; Leber's hereditary optic neuropathy; schizophrenia; mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS); cancer; psoriasis; hyperproliferative disorders; mitochondrial diabetes and deafness (MIDD) and myoclonic epilepsy ragged red fiber syndrome.

(M1) is useful for detecting altered MISP translocation in response to one or more translocation-inducing agents in cells transfected with MISP fusion polypeptides, its mutants or deletions, permits correlation of the presence of a particular MISP structural domain with the particular mitochondrial or cellular function of event. (M1) is also useful for detecting loss of MISPs, activation of one or more caspases as a downstream event in a apoptotic signaling cascade for cell death and any other phenotypic, biochemical, biophysical, metabolic, respiratory or other useful parameter which may depend on MISP translocation. The methods are also useful for evaluating the activity of compounds such as cell-permeant Ca^{++} . (IV) is useful for preparing binding partners and antibodies that specifically bind to the fusion polypeptide.

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FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B04-E08; B04-F01; B04-F0100E; B04-G01; B04-N04;
B05-A01B; B11-C08E1; B12-K04E; B14-H01; B14-H01B;
B14-J01A3; B14-J01A4; B14-J01B3; B14-J06; B14-N03;
B14-N16; B14-N17C; B14-S04; D05-H09; D05-H12A;
D05-H12E; D05-H14B2; D05-H17A6

TECH UPTX: 20010508

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: Preparation of (IV) is by standard recombinant techniques (claimed).

Preferred Method: In (M1), the mitochondrion is present with in a permeabilized neural, neuroblastoma (an SHSY5Y) cell or a cybrid cell. The permeabilized cell is depleted of cytosol. The cell comprises a nucleic acid expression construct comprising a promoter operably linked to a polynucleotide encoding a Bcl-2 family member such as Bcl-2, Bcl-XL, Bcl-w, Mcl-1, A1, NR-13, BHRF1, LMW5-HL, open reading frame (ORF)16, Ks-Bcl-2, E1B-19K or Ced-9.

(I) is an apoptogen or an agent that causes necrosis. The apoptogen is a pro-oxidant such as hydrogen peroxide, tert-butylhydroperoxide or peroxyxynitrite, or a calcium ionophore such as ionomycin. The apoptogen is preferably **atractyloside**, bongkreikic acid, thapsigargin, glutamate, N-methyl-D-aspartic acid, carbachol or ionomycin. MISP is (preferably) adenylate kinase-2 or cytochrome C or sulfide oxidase. The

affinity domain is a hemagglutinin epitope tag, a FLAG(RTM) epitope tag, an XPRESS(TM) epitope tag, a myc epitope tag or a polyhistidine epitope tag, a hemagglutinin epitope tag.

The detectable ligand employed in the methods is a monoclonal, polyclonal or single chain antibody comprising a fusion protein. The sample comprises a polypeptide that is a Bcl-2 family member as described above.

Preferred Expression Construct: The affinity domain of the fusion polypeptide encoded by the polynucleotide in (II), comprises less than 20 amino acids.

Preferred Host Cell: (III) further comprises a nucleic acid expression construct encoding a Bcl-2 family polypeptide as described above.

Preferred Composition: (V) comprises a 96-well microtiter plate or 386-well microtiter plate for high throughput screening of agents and compounds.

ABEX UPTX: 20010508

WIDER DISCLOSURE - The truncated MISP polypeptides, deletion mutants of MISP, fragments and variants are also disclosed.

ADMINISTRATION - (I) is administered through oral, topical, parenteral, sublingual, rectal, vaginal or intranasal routes. No specific clinical dosages are given.

EXAMPLE - Mechanistic studies regarding the conditions under which cytochrome c can be released in response to Ca^{2+} led to the discovery that release of the protein from mitochondria can, under certain conditions, occur independently of mitochondrial permeability transition. SH-SY5Y neuroblastoma cells overexpressing HA-tagged adenylate kinase 2 (AK2) were permeabilized with digitonin in a multiparameter in KCl-medium. Ca^{2+} was then added, and the cells were incubated at ambient temperature in the multiparameter chamber. In the absence of ATP and Mg^{2+} , relatively, conventional mitochondrial permeability transition (MPT)-like behavior was detected in multiparameter tracing and indicated by a drop in membrane potential in response to 300 μM Ca^{2+} used, or cyclosporin A present. The multiparameter tracings of extramitochondrial Ca^{2+} also suggested conventional MPT-like behavior. Similarly, there was a decrease in light scattering following Ca^{2+} accumulation, unless a lower concentration (100 μM) of Ca^{2+} was used, or unless cyclosporin A was present. When ATP (3 mM) and Mg^{2+} (4mM) were present, behaviors normally associated with MPT were not seen referred to as non-MPT conditions. In response to the highest load of Ca^{2+} (1.2 mM), the mitochondria reestablished some membrane potential. Moreover, the mitochondria were able to take up most of the added Ca^{2+} and demonstrated an increase only in light scattering. The suspensions were then centrifuged, and the pellets and supernatants were assayed for cytochrome c and HA-tagged AK2 release by Western blot analysis. The results of the Western analyzes confirmed that, in the absence of ATP and Mg^{2+} low (100 μM) and high (300 μM) levels of Ca^{2+} the release of cytochrome c as well as HA-tagged AK2 was stimulated. Western analyzes of extracts from cells treated under non-MPT conditions indicated that high (greater than 120 μM) levels of Ca^{2+} enhanced the release of cytochrome c from mitochondria, but did not enhance AK release. The released cytochrome c represented a fraction of the total cytochrome c pool. Thus mitochondrial permeability transition may occur via the formation of a multimolecular complex, the MPT pore. It has been proposed that the MPT pore comprises one or more isoforms of the adenine nucleotide translocator (ANT) protein. Two agents that bind to ANT and influence ANT conformation, bongkrekic acid (BKA) and **carboxyatractyloside** (CAtr), were assessed for their ability to alter cytochrome c release under the non-MPT conditions. The results showed that the addition of Ca^{2+} induced a large immediate increase in light scattering. This initial increase was followed by a slow decrease in light scattering that may be associated with some mitochondrial swelling;

neither BkA nor CAttr markedly altered these changes in light scattering. Such a slow decrease did not reflect MPT. The Western blot analysis showed that, under these conditions CAttr, induced a profound increase in cytochrome c release whereas BkA did not. These results provide evidence that agents that are capable of altering the conformation of **ANT** influenced cytochrome c release under conditions that did not promote MPT.

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